- **Spot urine samples** (if 24-h urine collection is difficult, for example, in non-toilet trained children)
    - Spot urine studies link the excretion rates to creatinine (limited because results may vary with collection time and patients' sex, body weight and age).

Timing of specific metabolic work-up

- stay on a self determined diet under normal daily conditions and should ideally be stone free.
- A **minimum of 20 days** is recommended (3 months suggested) **between stone expulsion or removal and 24-h urine collection**.
- Follow-up studies are necessary in patients receiving recurrent stone prophylaxis.
    - The first follow-up 24-h urine measurement at 8-12 weeks after starting drug prevention of stone recurrence.
    - Once urinary parameters have been normalised, it is sufficient to perform 24-h urine evaluation every 12 months.

Reference ranges of laboratory values

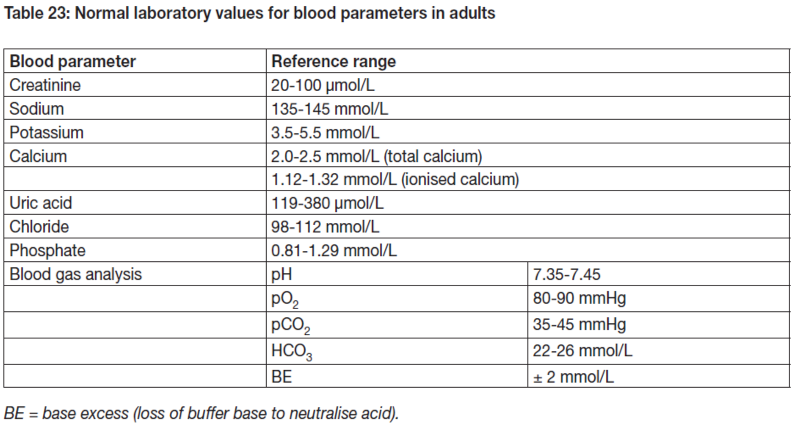


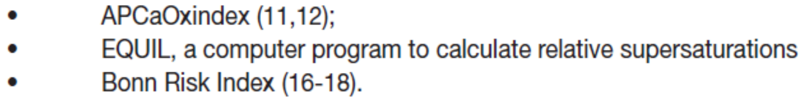
Table 23: Normal laboratory values for blood parameters in adults

Blood parameter	Reference range	
Creatinine	20-100 µmol/L	
Sodium	135-145 mmol/L	
Potassium	3.5-5.5 mmol/L	
Calcium	2.0-2.5 mmol/L (total calcium)	
	1.12-1.32 mmol/L (ionised calcium)	
Uric acid	119-380 µmol/L	
Chloride	98-112 mmol/L	
Phosphate	0.81-1.29 mmol/L	
Blood gas analysis	pH	7.35-7.45
	pO_2	80-90 mmHg
	pCO_2	35-45 mmHg
	HCO_3	22-26 mmol/L
	BE	± 2 mmol/L

BE = base excess (loss of buffer base to neutralise acid).

Risk indices and additional diagnostic tools

describe the crystallisation risk for Ca oxalate or Ca phosphate in urine:



- APCaOxindex (11,12);
- EQUIL, a computer program to calculate relative supersaturations
- Bonn Risk Index (16-18).

Table 24: Normal laboratory values for urinary parameters in adults

Urinary Parameters	Reference ranges and limits for medical attention
pH	Constantly > 5.8
	Constantly > 7.0
	Constantly ≤ 5.8
Specific weight	> 1.010
Creatinine	7-13 mmol/day females
	13-18 mmol/day males
Calcium	> 5.0 mmol/day
	≥ 8.0 mmol/day
Oxalate	> 0.5 mmol/day
	0.45-0.85 mmol/day
	≥ 1.0 mmol/day
Uric acid	> 4.0 mmol/day (women), 5 mmol/day (men)
Citrate	< 2.5 mmol/day
Magnesium	< 3.0 mmol/day
Inorganic phosphate	> 35 mmol/day
Ammonium	> 50 mmol/day
Cystine	> 0.8 mmol/day

Table 25: Normal values for spot urine samples: creatinine ratios (solute/creatinine) (20)

Parameter/Patient age	Ratio of solute to creatinine	
Calcium	**mol/mol**	**mg/mg**
< 12 months	< 2	0.81
1-3 years	< 1.5	0.53
1-5 years	< 1.1	0.39
5-7 years	< 0.8	0.28
> 7 years	< 0.6	0.21
Oxalate	**mmol/mol**	**mg/g**
0-6 months	< 325-360	288-260
7-24 months	< 132-174	110-139
2-5 years	< 98-101	80
5-14 years	< 70-82	60-65
> 16 years	< 40	32
Citrate	**mol/mol**	**g/g**
0-5 years	> 0.25	0.42
> 5 years	> 0.15	0.25
Magnesium	**mol/mol**	**g/g**
	>0.63	>0.13
Uric acid	< 0.56 mg/dl (33 ìmol/l) per GFR (ratio x plasma creatinine	
> 2 years		

Table 26: Urinary excretion of soluble excretion in 24-h urine samples**

Calcium excretion		Citrate excretion		Cystine excretion		Oxalate excretion		Urate excretion	
All age groups	< 0.1 mmol/kg/24 h < 4 mg/kg/24 h	All age groups	Boys > 1.9 mmol/1.73 m^2/24 h > 365 mg/1.73 m^2/24 h	< 10 y	< 55 µmol/1.73 m^2/24 h < 13 mg/1.73 m^2/24 h	All age groups	< 0.5 mmol/1.73 m^2/24 h < 45 mg / 1.73 m^2/24 h	< 1 y	< 70 µmol/kg/24 h < 13 mg/kg/24 h
			Girls > 1.6 mmol/1.73 m^2/24 h > 310 mg/1.73 m^2/24 h	> 10 y	< 200 µmol/1.73 m^2/24 h < 48 mg/1.73 m^2/24 h			1-5 y	< 65 µmol/kg/24 h < 11 mg/kg/24 h
								> 5 y	< 55 µmol/kg/24 h < 9.3mg/kg/24 h

***24h urine parameters are diet and gender dependent and may vary geographically.*

General and Specific measures for Stone treatment and recurrence prevention

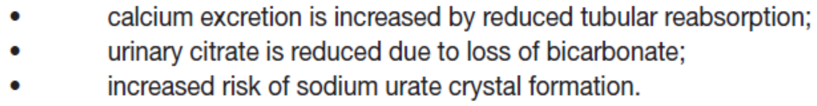
General considerations: انظر الرسم

- All stone formers, independent of their individual risk, should follow the preventive measures below.
- Main focus is ***normalisation of dietary habits and lifestyle risks***.
- **Stone formers at high risk need specific prophylaxis for recurrence, which is usually pharmacological treatment and based on stone analysis**.

Diet

- A common sense approach to diet should be taken, that is, a mixed balanced diet with contributions from all food groups, but without any excesses.
  - ***Fruits, vegetables and fibres***:
    - encouraged because of the beneficial effects of fibre
    - alkaline content of a vegetarian diet ↑ urinary pH.
  - ***Oxalate***:
    - Limit excessive intake of oxalate-rich to prevent high oxalate load, particularly in patients who have high oxalate excretion.
  - ***Vitamin C:***
    - although vitamin C is a precursor of oxalate, its role as a risk factor in calcium oxalate stone formation remains controversial.
    - However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

- ***Animal protein***
    - should not be taken in excess (11,12) and limited to 0.8-1.0 g/kg body weight.
    - Excessive consumption of animal protein has several effects that favour stone formation, including hypocitraturia, low urine pH, hyperoxaluria and hyperuricosuria.
- ***Calcium intake***
    - should not be restricted unless there are strong reasons because of the inverse relationship between dietary calcium and stone formation
    - The daily Ca requirement is 1000-1200 mg/day
    - Calcium supplements are not recommended except in enteric hyperoxaluria, when additional calcium should be taken with meals to bind intestinal oxalate.
- ***Sodium***:
    - the daily sodium (NaCl) intake should not exceed 3-5 g. High intake adversely affects urine composition:



- calcium excretion is increased by reduced tubular reabsorption;
- urinary citrate is reduced due to loss of bicarbonate;
- increased risk of sodium urate crystal formation.

    - Calcium stone formation can be reduced by restricting sodium and animal protein
- *Urate*:
    - Restrict intake of urate-rich food (<500 mg/d) in pts with hyperuricosuric Ca oxalate and uric acid stones.

Lifestyle

Lifestyle factors may influence the risk of stone formation, for example, overweight and obesity. Another risk factor is arterial hypertension

Selective medical therapies for stones

تجميعة للعلاج كله سيتم ذكر
كل حاجه في مكانها فيما بعد

1) Absorptive hypercalciuria

mainly for type 1 } type 2 often ok with decreased Ca diet + increased fluids alone

- **Thiazides (1st line)**
    - Mech:
        - stimulates Ca resorption in DCT & promotes Na excretion
        - decreases serum K and mildly decreases urinary citrate
        - **doesn't change gut absorption of Ca } low long-term success**
    - **combined with K citrate + dietary restriction of Ca & oxalate**
    - Use:
        - chlorthalidone, indapamide, trichlormethidazide, amiloride + HCTZ
    - S/Es
        - **hypoK**, muscle cramps, **hyperuricosuria**, **hypocitraturia**, ↓'d libido, sleepiness
        - may unmask or induce primary hyperPTH'ism
- **C**ellulose PO4
    - Mech:
        - binding resin that ↓'s Ca absorption
        - also binds to Mg (need supplements)
    - **only recommended if refractory to thiazides, due to +++ GI S/Es**
    - S/Es: **hypoMg, hyperoxaluri**a, PTH stimulation, GI distress
- **O**rthophosphate } inhibits Vit D3
    - Mech:
        - ↓'s GI absorption of Ca & urinary Ca excretion + ↓'s urine Ca-oxalate saturation
        - ↑'s urine PO4 (**contraindicated in struvite stones**), oxalate & citrate
    - **recommended only if refractory to other methods**
    - S/Es
        - PTH stimulation, hyperoxaluria, GI distress, soft tissue calcification
- **B**ran (rice)
    - may decrease intestinal Ca absorption and increase urine PO4 excretion

2) Renal leak hypercalciuria

- **thiazides**
    - ideal because it increases reabsorption of Ca in distal & proximal tubule
    - **also give K citrate (K supplementation + increases urine citrate)**
    - does have **good long-term success**

3) Resorptive (primary hyperPTH) hypercalciuria

- **PTHectomy**
    - resection of dominant adenoma or removal of all 4 hyperplastic glands
    - decreases urinary Ca, gut absorption of Ca, and serum Ca

4) Hypocitraturic Ca stones

- **alkalinization**
    - distal RTA → **K citrate** } corrects metabolic acidosis & hypoK while ↑'ing urinary citrate
    - chronic diarrheal states → **liquid K citrate** } faster absorption to offset rapid GI transit
        - corrects acidosis from HCO3 loss & ↑'s urinary citrate
    - thiazide-induced →**add K citrate** } supplements lost K and increases urinary citrate
    - high protein diet → improve diet
    - idiopathic → **K citrate** } increases urinary citrate

5) Hyperuricosuric Ca stones

- decreased dietary purine intake
- **allopurinol**
    - Mech:
        - inhibits xanthine oxidase, which converts xanthine to uric acid
        - ↓'s serum & urine uric acid thereby ↓'ing nucleation of Ca oxalate cry
    - S/Es: rash, myalgia
- **K citrate**
    - Mech: increases urine pH & urinary citrate
    - S/Es: **hyperK, GI upset**

6) Hyperoxaluric Ca stones

increased fluids for all

a) Enteric

- **hydration + low oxalate, low fat diet**
- **Ca supplements**
  - Mech:
    - binds oxalate in gut & prevents absorption BUT also get hypercalciuria
- **cholestyramine**
  - Mech:
    - binds bile salts thereby ↓'ing colonic hyperabsorption of oxalate
- **K citrate or Mg citrate** }
  - **Mech:**
    - corrects hypoK + increases urine citrate (and Mg)

b) primary

- **pyridoxine (B6)**
  - Mech:
    - ofactor in conversion of glyoxylate to glycine & ↓'s oxalate excretion
  - S/Es: diarrhea, neurotoxicity (with high doses)
- **increased H2O intake, K citrate, thiazides, Mg gluconate**
- **need combined liver and kidney Tx**

c) dietary

- **decrease dietary oxalate intake**

7) Hypomagnesiuric Ca stones

also characterized by hypocitraturia + low urine volume

- **Mg oxide / Mg hydroxide**
  - ↑'s urine Mg & citrate, ↓'s urine oxalate (given with K citrate)
  - S/Es GI upset **(lots of diarrhea)**
- **K-Mg citrate:** may be better tolerated from GI perspective with same effects

8) Gout

goal is to increase urine pH above 5.5 (but not too alkaline □ preferably 6.5 – 7.0)

- Na bicarb } increases pH of urine BUT can lead to Ca stones
- **K citrate** } ↑'s urine pH & ↑'s citrate (no increase in Ca stones)
- **add allopurinol if** urine uric acid excretion is ↑'d or if hyperuricemia exists

9) cystinuria

- **hydration } aim for 2-3 L of u/o per day**
    - **} try to decrease urine [ ] of cystine to <250mg/L**
- **low-Na diet** } high dietary salt leads to increased cystine excretion
- **chelators**
    - a. **Penicillamine-D**
        - increases cystine solubility in urine by binding to cystine S-S bonds
        - (Cuprimine) } **more frequent side effects but also slightly more effective**
        - S/Es □ nephrotic syndrome, dermatitis, **pancytopenia**
    - b. α-**mercaptopropionylglycine**
        - ↑'s cystine solubility by binding to it (S-S bonds)
        - (Thiola) } **less frequent side effects (1st line)**
        - S/Es □ rash, asthenia, GI, joint aches, mental status Δ's
    - c. **C**aptopril
        - ACEi that increases cystine solubility by binding to it (S-S bonds)
        - } **least frequent side effects but also least effective**
        - S/Es □ fatigue, hypoTN, chronic cough, rash
    - d. **B**ucillamine
        - chelator only available in ASIA
- alkanizers
    - i. **K** citrate
        - increases urine pH to decrease cystine crystal formation
        - but pKa is 8.3 so its hard and at these levels, at risk of Ca PO4 stones
    - ii. **M**ucomyst
    - iii. **A**cetazolamide

10) struvite stones

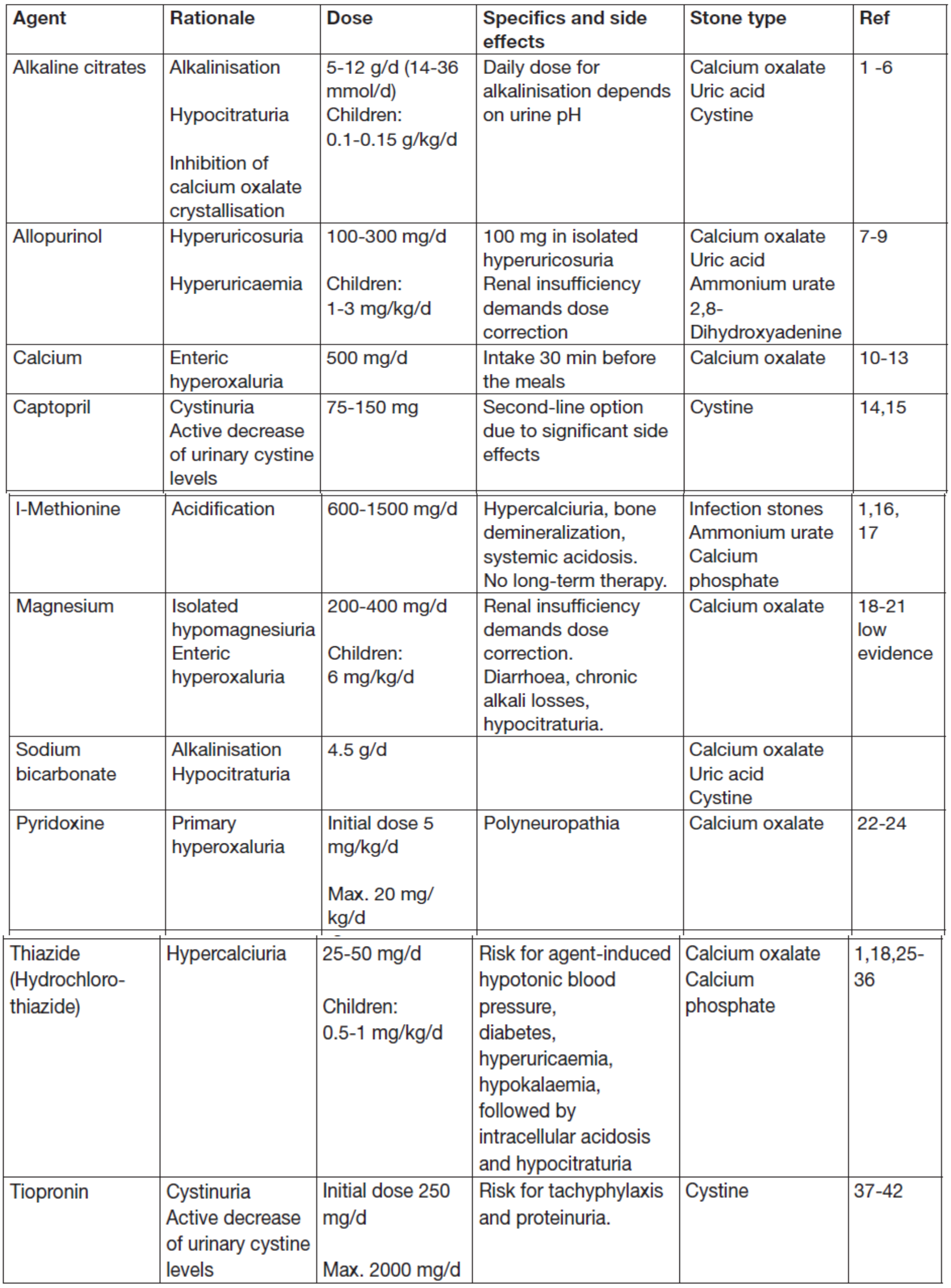
- **surgical management of ALL stone burden**
  - followed by improved bladder health,
  - adequate urinary drainage, and suppressive Abx **(remove then prevent)**
- acetohydroxamic
  - urease inhibitor
  - acid } **for severe cases** □ prevents recurrence and inhibits growth
  - } side effects are frequent (20-60%)
  - S/Es □ **DVT (15%)**, tremor, H/A, palpitations, edema, rash, GI upset, anemia
- hemiacidrin (Renacidin)
  - irrigant for dissolution of residual fragments
  - **NS pre-irrigation x 24hrs followed by solution at 120 cc/hr**
    - **} not used often due to risk of sepsis & death**

Stone-specific metabolic evaluation and pharmacological recurrence prevention

Introduction

Pharmacological treatment is **necessary in patients at high risk** for recurrent stone. Ideal drug halt stone formation, have no side effects, and be easy to administer.

Table 28: Pharmacological substances used for stone prevention - characteristics, specifics and dosage



Agent	Rationale	Dose	Specifics and side effects	Stone type	Ref
Alkaline citrates	Alkalinisation Hypocitraturia Inhibition of calcium oxalate crystallisation	5-12 g/d (14-36 mmol/d) Children: 0.1-0.15 g/kg/d	Daily dose for alkalinisation depends on urine pH	Calcium oxalate Uric acid Cystine	1 -6
Allopurinol	Hyperuricosuria Hyperuricaemia	100-300 mg/d Children: 1-3 mg/kg/d	100 mg in isolated hyperuricosuria Renal insufficiency demands dose correction	Calcium oxalate Uric acid Ammonium urate 2,8-Dihydroxyadenine	7-9
Calcium	Enteric hyperoxaluria	500 mg/d	Intake 30 min before the meals	Calcium oxalate	10-13
Captopril	Cystinuria Active decrease of urinary cystine levels	75-150 mg	Second-line option due to significant side effects	Cystine	14,15
l-Methionine	Acidification	600-1500 mg/d	Hypercalciuria, bone demineralization, systemic acidosis. No long-term therapy.	Infection stones Ammonium urate Calcium phosphate	1,16, 17
Magnesium	Isolated hypomagnesiuria Enteric hyperoxaluria	200-400 mg/d Children: 6 mg/kg/d	Renal insufficiency demands dose correction. Diarrhoea, chronic alkali losses, hypocitraturia.	Calcium oxalate	18-21 low evidence
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/d		Calcium oxalate Uric acid Cystine	
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/d Max. 20 mg/ kg/d	Polyneuropathia	Calcium oxalate	22-24
Thiazide (Hydrochloro-thiazide)	Hypercalciuria	25-50 mg/d Children: 0.5-1 mg/kg/d	Risk for agent-induced hypotonic blood pressure, diabetes, hyperuricaemia, hypokalaemia, followed by intracellular acidosis and hypocitraturia	Calcium oxalate Calcium phosphate	1,18,25-36
Tiopronin	Cystinuria Active decrease of urinary cystine levels	Initial dose 250 mg/d Max. 2000 mg/d	Risk for tachyphylaxis and proteinuria.	Cystine	37-42

Stone Formation

Mechanisms, diagnosis of causative factors and medical ttt for specific stone types.

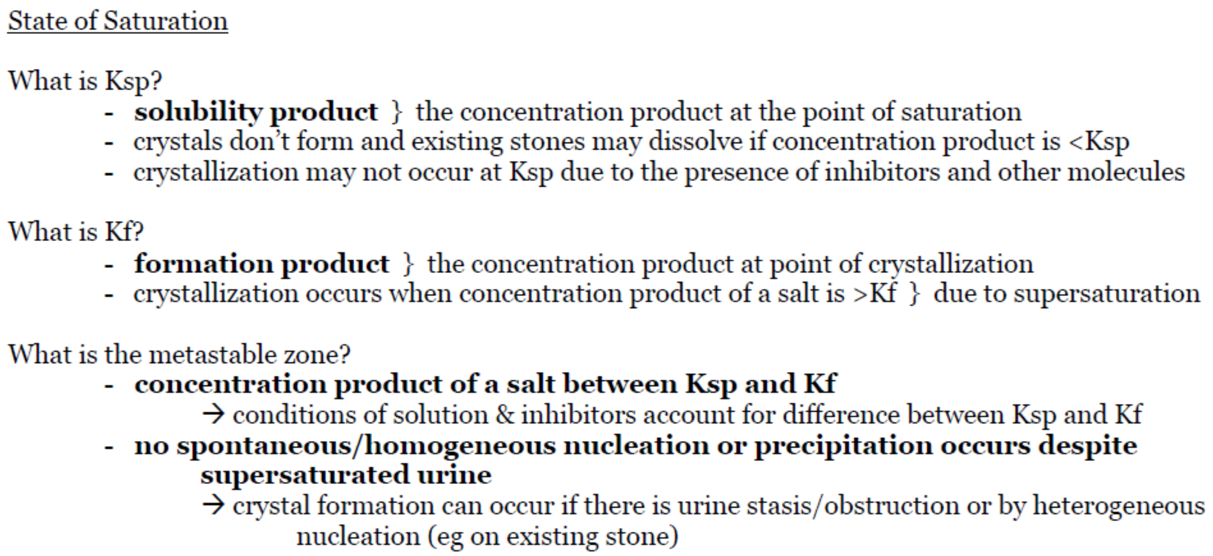
- Result of a complex process = metabolic + anatomic factors + inf.
- **Calcium, oxalate, uric acid or cystine** molecules may develop into stones when they are supersaturated in urine.

➢ ^{1} a supersaturated solution, ^{2} a dec. conc. of crystallisation inhibitors (citrate, magnesium, pyrophosphate, macromolecules and glycosaminoglycans) → stone formation.

➢ Urinary pH changes also affect stone formation.

➢ An impaired flow of urine due to an abnormal morphology → stasis → increase the concentration of stone-forming substances.

Pathophysiology of stone formation



State of Saturation

What is Ksp?

- **solubility product** } the concentration product at the point of saturation
- crystals don't form and existing stones may dissolve if concentration product is <Ksp
- crystallization may not occur at Ksp due to the presence of inhibitors and other molecules

What is Kf?

- **formation product** } the concentration product at point of crystallization
- crystallization occurs when concentration product of a salt is >Kf } due to supersaturation

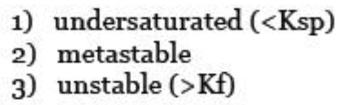
What is the metastable zone?

- **concentration product of a salt between Ksp and Kf**
  → conditions of solution & inhibitors account for difference between Ksp and Kf
- **no spontaneous/homogeneous nucleation or precipitation occurs despite supersaturated urine**
  → crystal formation can occur if there is urine stasis/obstruction or by heterogeneous nucleation (eg on existing stone)

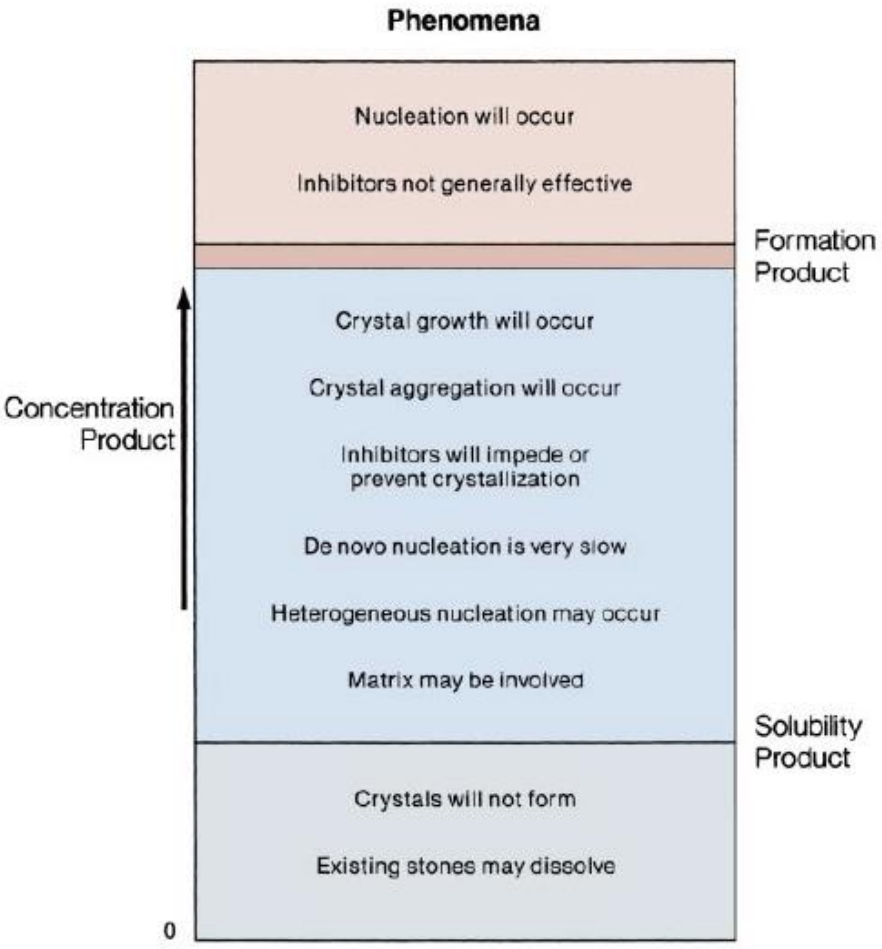
Relative saturation ratio = conc. product of urine /Ksp of specified stone-forming salt

(the higher the ratio, the more likely the crystallization/precipitation of the salt)

3 major states of urine saturation:



1) undersaturated (<Ksp)
2) metastable
3) unstable (>Kf)


Phenomena
Nucleation will occur
Inhibitors not generally effective
Formation Product
Crystal growth will occur
Crystal aggregation will occur
Inhibitors will impede or prevent crystallization
De novo nucleation is very slow
Heterogeneous nucleation may occur
Matrix may be involved
Concentration Product
Solubility Product
Crystals will not form
Existing stones may dissolve
0

Nucleation and Crystal Growth, Aggregation, and Retention

- “**homogeneous nucleation**”:
  - de novo formation of stone nucleus } only occurs >Kf
  - nuclei are the earliest crystal structures that WON”T dissolve
  - if transit time through nephron is slow and supersaturation level is adequate, nuclei persist and grow (“free crystal particle growth”)
  - inhibitors (eg citrate) destabilize nuclei, promoters stabilize nuclei.
  - if enough nuclei form and grow, they aggregate to form a stone.

- “**heteregeneous nucleation**:
  - microscopic impurities or other urine constituents (epithelial cells, cell debris, casts, RBCs, other crystals) can facilitate nucleation by adsorption of the crystal components
  - requires less energy than homogeneous nucleation } can occur if >Ksp

- Role of papillary plaques (**Randall’s plaques**) in stone formation:
  - much more common in stone formers } 75% vs 40%.
  - urine is most supersaturated in the renal papilla.
  - Mech.
    - injury to vasa recta near renal papilla.
    - repair of wall involves atherosclerotic-like reaction leading to calcification.
    - calcification erodes into collecting duct where it serves as a nidus for stones.
  - Other theory:
    - Ca apatite (PO4) plaques originate in BM of thin loops of Henle.
    - plaque extends through interstitium to subepithelial location.
    - once they erode through urothelium, they act as a nidus for stone nucleus.

Inhibitors and Promoters of Crystal Formation

- ***urinary stone inhibitors:***

  (no known inhibitors that affect uric acid crystallization)

  - **Examples:**
    - **Citrate } most potent complexor of Ca**
    - **Tamm-Horsfall glycoprotein** (made in TAL & DCT) (most abundant protein in urine & most potent stone aggregation inhibitor
    - **Urine prothrombin fragment 1** (most potent inhibitor in normal urine)
    - **GAG** (can occasionally act as promoter of crystal nucleation)
    - **Glucosamine**
    - Nephrocalcin glycoprotein (made in PCT & TAL)
    - Acid mucopolysaccharides
    - Magnesium, Inorganic phosphate
    - **O**steopontin/uropontin, **B**ikunin.
  - Mech. Of action of urinary stone inhibitors:

    inhibits **nucleation, growth, aggregation**

Stone matrix

- the non-crystalline portion of stone (~2.5% of total Stone weight)
- pure matrix stone } ~ 65% of stone, when associated with UTIs
- composed of glycoprotein (65%), non-amino sugars, bound water, organic ash, **Substance A** and glucosamine
- E. coli may increase matrix formation

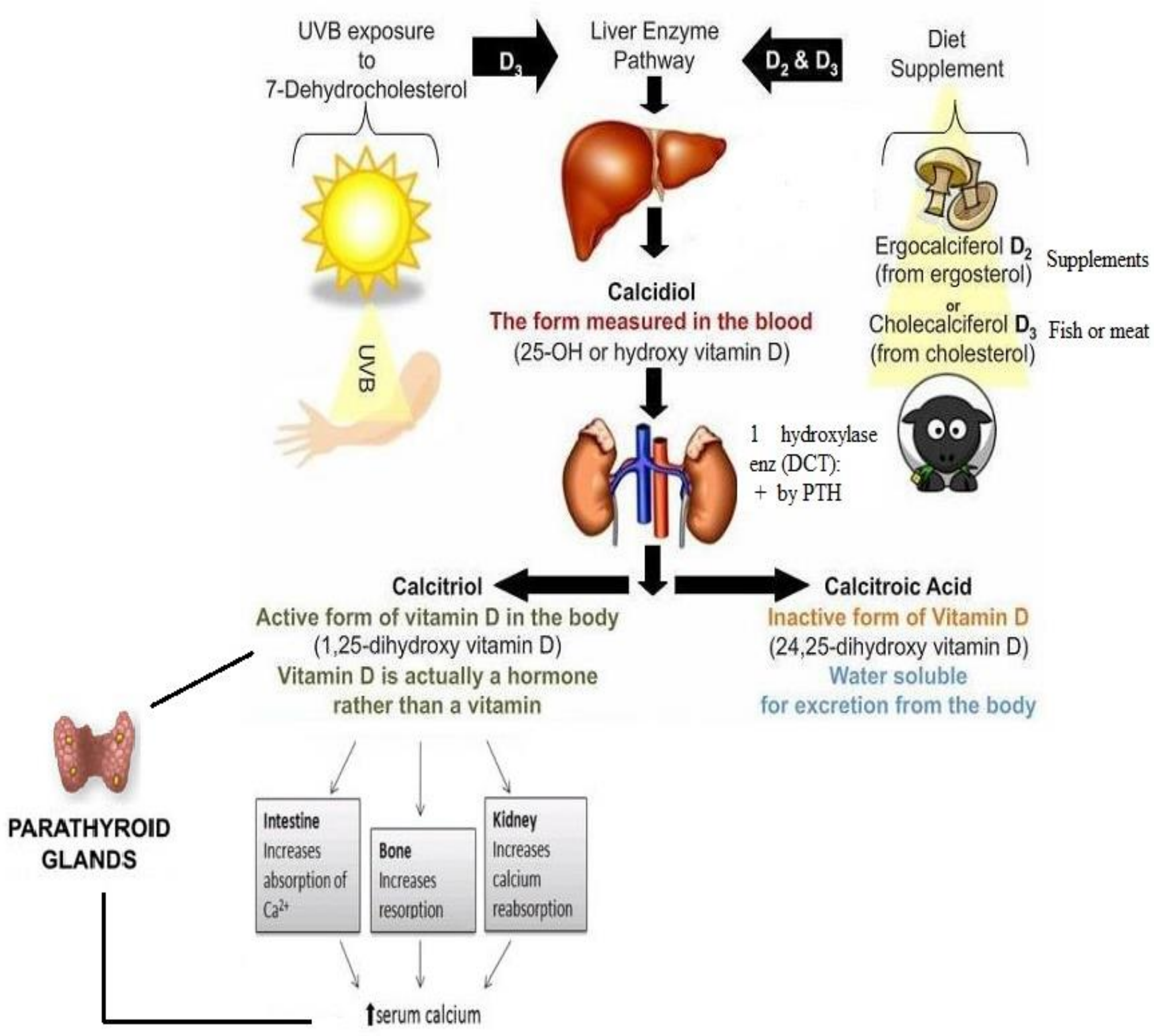
Metabolic abnormalities leading to stone formation

1. **Ca-containing (75%)**
- Ca oxalate monohydrate – COM (whewellite) (60%)
- Ca oxalate dihydrate (weddellite)
- Mixed Ca oxalate + hydroxyapatite (20%)
- Ca PO4 (brushite) (2%)

2. **non-Ca stones (25%)**
- Uric acid (7%)
- Mg NH4 PO4 (struvite) (7%)
- Cystine (2%)
- Matrix (<1%)
- 2,8-dihydroxyadenine (<1%)
- medication related (triamterene (<1%), silica (<1%), indinavir (<1%), etc

Calcium stones

Vit. D Synthesis

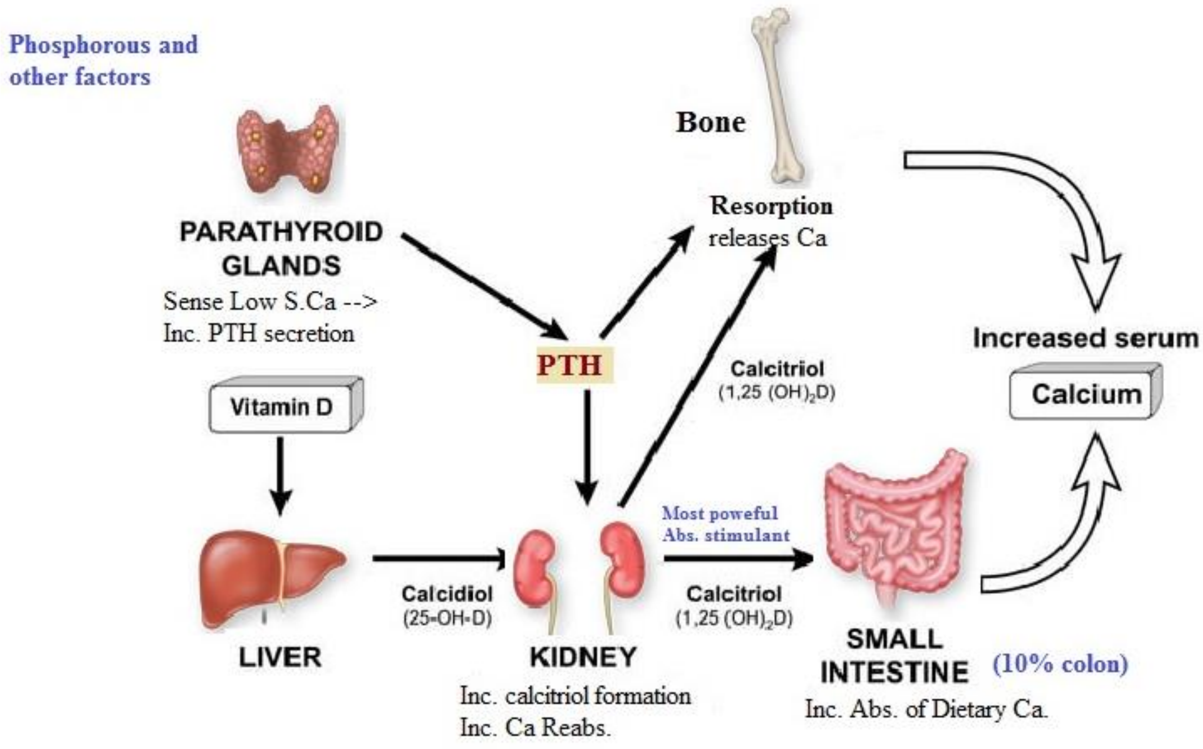

UVB exposure to 7-Dehydrocholesterol
D_3
Liver Enzyme Pathway
D_2 & D_3
Diet Supplement
UVB
Ergocalciferol D_2 (from ergosterol)
Supplements
or
Cholecalciferol D_3 (from cholesterol)
Fish or meat
Calcidiol
The form measured in the blood
(25-OH or hydroxy vitamin D)
1 hydroxylase enz (DCT):
+ by PTH
Calcitriol
Active form of vitamin D in the body
(1,25-dihydroxy vitamin D)
Vitamin D is actually a hormone rather than a vitamin
Calcitroic Acid
Inactive form of Vitamin D
(24,25-dihydroxy vitamin D)
Water soluble
for excretion from the body
PARATHYROID GLANDS
Intestine
Increases absorption of Ca^{2+}
Bone
Increases resorption
Kidney
Increases calcium reabsorption
↑serum calcium

- sunlight converts 7-dehydrocholesterol in skin to previtamin D3
- previtamin D3 is brought to liver and hydroxylated to 25-(OH)Vitamin D3 (calcidiol)
- once in the kidney, 25-(OH)Vitamin D3 is **hydroxylated by 1α-hydroxylase in PCT** to 1, 25-dihydroxyvitamin D3 (calcitriol) → stimulated by PTH
- Vitamin D is also synthesized by macrophages

What are the effects of 1, 25-dihydroxyvitamin D3 (calcitriol)?

1) gut → increased absorption of Ca & Mg
2) PTH gland → decreased PTH production
3) bone → increased Ca resorption
4) kidney → increased reabsorption of Ca

Ca metabolism:



- 30-40% of dietary Ca absorbed in gut → **90% small bowel & 10% colon**
- Ca absorption varies with intake → low fractional absorption with high Ca diet
- Ca absorption reduced by intestinal complexors } PO4, citrate, oxalate, sulfate, and fatty acids
- **active Vit D made in kidney is most potent stimulator of gut absorption of Ca**
  → active 1,25-VitD3 upregulated by PTH via 1α-hydroxylase
- 60% of Ca filtered by kidney } PCT reabsorbs 65%
  } 10% reabsorbed in DCT (stimulated by PTH)

PTH effect:

- **low serum Ca stimulates PTH production**
- Mg inhibits PTH excretion

1) Bone: Increased Ca/PO4 resorption (osteoclast activation)
2) Kidney:
   - Vit. D production } stimulates 1α-hydroxylase to convert 25-VitD3 to active 1,25(OH)2D3 **(PTH does not have direct effect on gut Ca absorption)**
   - Ca reabsorption from kidneys } occurs in DCT
   - inhibits PO4reabsorption } occurs in PCT

Etiologic classification of stones:

A) Ca Containing stones: most common metabolic abnormality associated with Ca stone formation are:

1. **Hypercalciuria (most common abn identified in Ca stone formers)**
    - absorptive Type I, II (**most common solely occurring abn'ity)**
    - renal leak: Na intake, Dent's, Bartter's, etc
    - resorptive } primary hyperPTH, etc
    - primary idiopathic } most common cause of pediatric stones
2. **hypocitraturic Ca stones** (10-50%)
    - related to systemic acidosis
    - distal RTA, chronic diarrheal syndrome, thiazide-induced, high protein diet, idiopathic
    - **tied for most common combined abn'ity**
3. **hyperuricosuric Ca stones** (10-40%)
    - dietary excess of purines (most common)
    - uric acid overproduction } gout, myeloproliferative d/o, MM, hemoglobinopathy, etc
4. **hyperoxaluric Ca stones** (2-15%)
    - primary oxalosis (AR)
    - enteric
    - dietary
    - idiopathic
5. **hypomagnesiuric Ca stones** (5-10%)
    - reduced intestinal absorption (IBD, malabsorption)
    - poor dietary intake

B) ***Non Ca containing:***

a. ***Gouty diathesis*** (15-30%)
    - normal urinary uric acid + acidic urine pH

b. Cystinuria
    - COLA } AR inheritance

c. Struvite

C) low urine volume stones (10-50%) } **tied for most common combined abN'ity**

D) no disturbance/miscellaneous

Hypercalciuria:

(most common abnormality found in Ca stone)

- **Def:**
  - > 4 mg/kg/day (excreted in Urine)
  - >**200mg**/day (after 400mg Ca and 100mg Na diet for 1 week)
- **Causes:**

2ry :

known etiology → produces excessive urinary calcium

1) Absorptive hypercalciuria:

   Causes that increase gastrointestinal hyperabsorption (hypervitaminosis D)
   - increased Ca excretion after oral Ca load
   - possibly related to Vit D receptor upregulation
   - type 1 } hypercalciuria **despite low** Ca diet (severe & less common)
   - type 2 } hypercalciuria only with high Ca diet (normal Ca excretion on restricted Ca diet)

2) Resorptive hypercalciuria (uncommon)

   Causes that increase bone resorption

   A. **associated with primary hyperPTH'ism**
      - high PTH → ↑'d gut absorption (Vit D) & ↑'d bone resorption
      - hyperCa present in most cases, but can rarely be N (then resembles renal leak)
      - Serum Ca worsen after "thiazide challenge" (if truly resorptive)

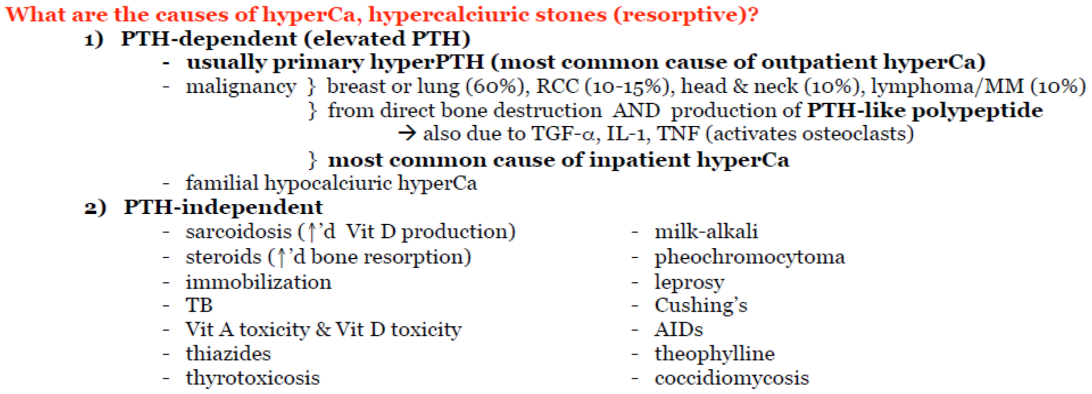
   B. Can be due to **malignancy** (↑ PTH), **sarcoid** (↑ Vit D), **TB, hyperT4, pheo**, **immobilization, acidosis** etc

3) Renal leak hypercalciuria
   - impaired **Ca reabsorption** (PCT) → secondary **hyperPTH'ism**
   - related to Na intake, PGs, genetic abnormalities (Dent's, Bartter's)
4) Primary idiopathic hypercalciuria (commonest cause of Ca stones in kids)

Idiopathic:

inv fail to find cause

	F Ur. Ca	S. Ca	PTH	Vit D
Absorptive	N	N	N or ↓	↑ (rec upreg.)
Resorptive	↑	↑	↑	↑
Renal leak	↑	N	↑	↑
1ry idiopathic				



What are the causes of hyperCa, hypercalciuric stones (resorptive)?

1) **PTH-dependent (elevated PTH)**
   - **usually primary hyperPTH (most common cause of outpatient hyperCa)**
   - malignancy } breast or lung (60%), RCC (10-15%), head & neck (10%), lymphoma/MM (10%)
     } from direct bone destruction AND production of **PTH-like polypeptide**
     → also due to TGF-α, IL-1, TNF (activates osteoclasts)
     } **most common cause of inpatient hyperCa**
   - familial hypocalciuric hyperCa
2) **PTH-independent**
   - sarcoidosis (↑'d Vit D production)
   - steroids (↑'d bone resorption)
   - immobilization
   - TB
   - Vit A toxicity & Vit D toxicity
   - thiazides
   - thyrotoxicosis
   - milk-alkali
   - pheochromocytoma
   - leprosy
   - Cushing's
   - AIDs
   - theophylline
   - coccidiomycosis

Dent's disease:

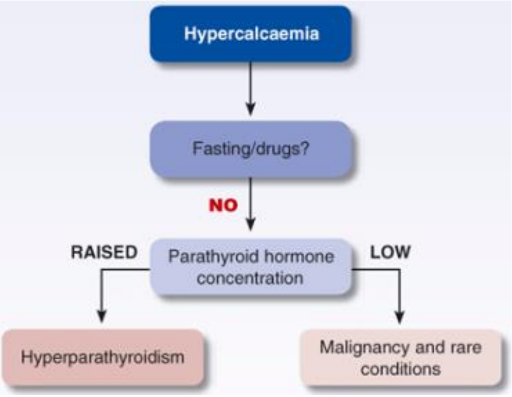
- X-linked recessive
- **microhematuria** + **LMW proteinuria** + **hypercalciuria** + **CRF** + **stones** + **nephrocalcinosis** (medullary)

Bartter's syndrome:

- AR genetic defect involving thick AL of kidney (can affect Na-K-Cl gene, K channel gene, Cl channel gene**)**
- get **hypoK, hypoCL, metabolic alkalosis**
- results in **hypercalciuria + stones**

Diagnosis:

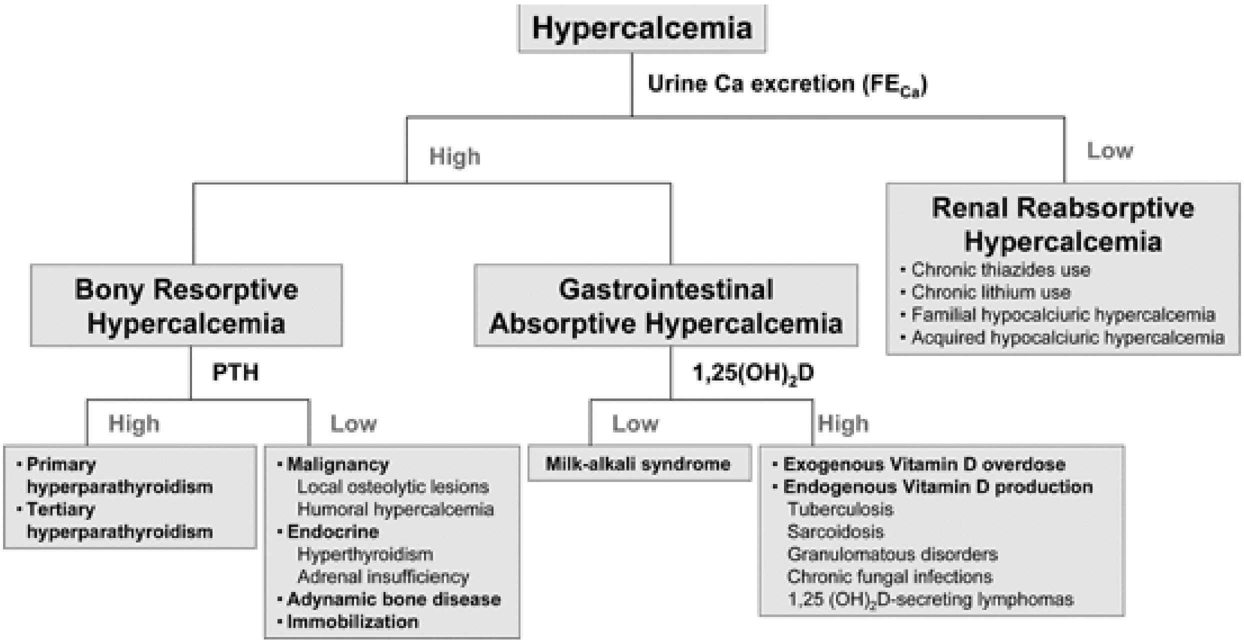
- A good ***screening test for hypercalciuria*** ***compares the ratio of urinary calcium to creatinine***.
  - Ur. Ca/ Cr ratio in children < 0.2.
    - higher → repeat testing is indicated. (Neonates and infants → higher calcium excretion and lower creatinine excretion)
    - follow-up ratios are normal→ no additional testing
    - if ratio remains elevated → a **timed 24-hour urine collection** and the **calcium excretion** calculated.
      - ***The 24-hour calcium excretion test*** is the criterion standard for the diagnosis of hypercalciuria.
      - ***Diagnosis confirmed if*** calcium excretion > 4 mg/kg/day
    - **Further evaluation:**
      - includes levels of serum bicarbonate, creatinine, alkaline phosphatase, calcium, magnesium, pH, and parathyroid hormone.


Hypercalcaemia
Fasting/drugs?
NO
RAISED
Parathyroid hormone concentration
LOW
Hyperparathyroidism
Malignancy and rare conditions

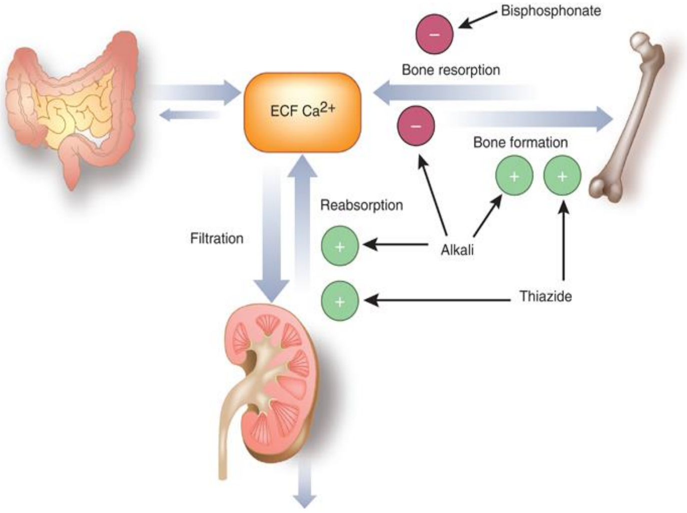
- **A 24-hour urine collection** should also be collected for measurement of **calcium, phosphorus, sodium, magnesium, citrate** and **oxalate**. Meanwhile dietary manipulations should be tried to normalise urine calcium.

Hypercalcuria Diagnosis Simplified test guidelines	**Urinary Calcium on 400-mg Calcium Diet (Normal = < 200 mg/24 h)**	**Fasting Calcium/Creatinine Ratio (Normal = < 0.11)**	**Post–Calcium Load Calcium/Creatinine Ratio (Normal = < 0.20)**
Normal	Normal	Normal	Normal
Absorptive type I	High	Normal	High
Absorptive type II	Normal	Normal	High
Absorptive type III (renal phosphate leak)	High	High	High
Renal leak	High	High	High
Resorptive (hyperparathyroidism)	High	High	High

Using Urine Ca excretion (FE_{Ca}) to diagnose the type of hypercalcuria:


Hypercalcemia
Urine Ca excretion (FE_{Ca})
High
Low
Renal Reabsorptive Hypercalcemia
• Chronic thiazides use
• Chronic lithium use
• Familial hypocalciuric hypercalcemia
• Acquired hypocalciuric hypercalcemia
Bony Resorptive Hypercalcemia
Gastrointestinal Absorptive Hypercalcemia
PTH
$1,25(OH)_2D$
High
Low
Low
High
• Primary hyperparathyroidism
• Tertiary hyperparathyroidism
• Malignancy
Local osteolytic lesions
Humoral hypercalcemia
• Endocrine
Hyperthyroidism
Adrenal insufficiency
• Adynamic bone disease
• Immobilization
Milk-alkali syndrome
• Exogenous Vitamin D overdose
• Endogenous Vitamin D production
Tuberculosis
Sarcoidosis
Granulomatous disorders
Chronic fungal infections
$1,25 (OH)_2D$-secreting lymphomas

Management:



1. General measures كالمعتاد

a. ***Dietary Na restriction*** & ***maintenance of Ca intake***. Trial of a low-Ca diet to determine if exogenous calcium intake is contributing to high Ur. Ca.

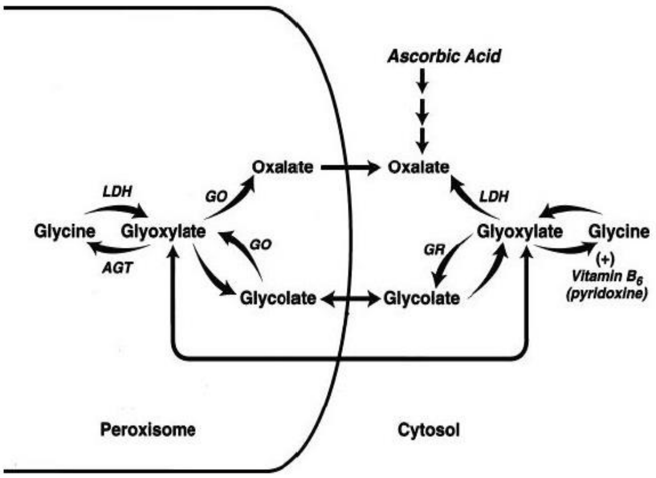
b. **Citrate therapy** with low citrate or if hypercalciuria persists, despite other ttt.

2. **Hydrochlorothiazide** and thiazide-type diuretics (1-2 mg/kg/day).

Hyperoxaluria.

Oxalic acid is a metabolite excreted by the kidneys.

Only 10-15% of oxalate comes from diet.



→ OXALATE METABOLISM PATHWAY

Hyperoxaluria:

Oxalate excretion > 0.5 mmol/d in adults (> 0.37 mmol/1 .73 m2/day in children) **> 40 mg/d**

Oxalate handling across the liver, stomach, intestinal tract, and kidney*:*

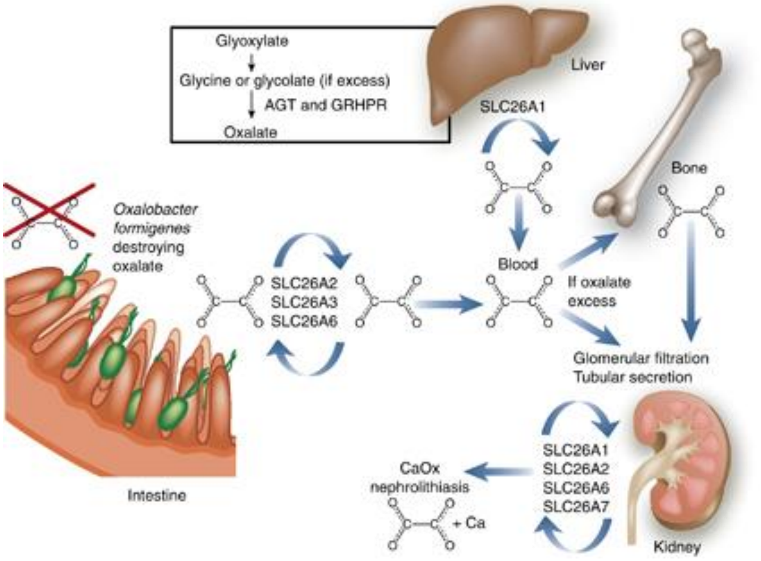
- Dietary oxalate is absorbed from the gut

The serum oxalate delivered from both exogenous and endogenous sources (gut and liver, respectively)

- rapidly excreted by the kidney, via both glomerular filtration and tubular secretion

- Oxalobacter formigenes is destroying oxalic acid and is able to induce oxalate secretion/excretion in the colon

- Excessive urinary concentrations of oxalate and calcium lead to development of calcium oxalate kidney stones.



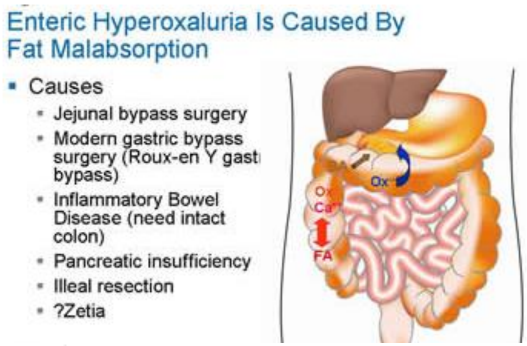
- Etiology:
  - Hyperoxaluria: result from increased dietary intake, enteric hyperabsorption (as in short bowel syndrome) or an inborn error of metabolism.

1) Dietary

- ↑'d oxalate-rich diet
  (nuts, chocolate, spinach, broccoli, strawberries, rhubarb, brewed tea)
- ↑'d Vit C diet
- may be d.t **absence of *Oxalobacter formigenes*** (oxalate-degrading bact.)

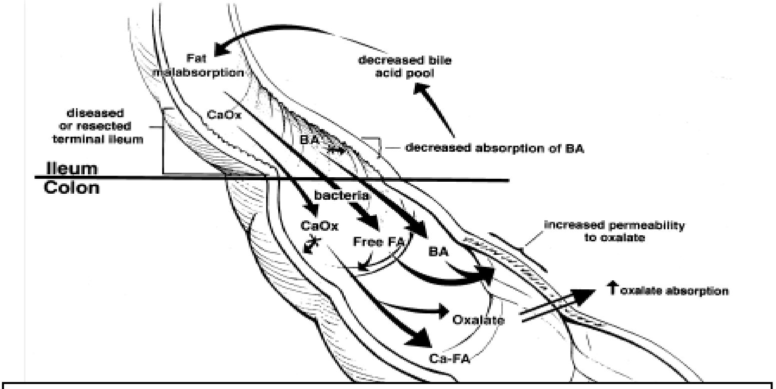
2) Enteric (most common acquired cause)

- chronic diarrheal states (Crohn's, Celiac sprue, short gut, small bowel resection, etc)
- Mech:
  - fat malabsorption results in saponification of FA's with Ca & Mg
  - → **↑'d oxalate available for absorption** d.t. ↓'d Ca/Mg complexing
  - malabsorbed FA's & bile salts **→ ↑'d oxalate absorption in colon too**
- also get **dehydration, hypoK, hypomagnesuria, hypocitraturia, acidic urine**



Enteric Hyperoxaluria Is Caused By Fat Malabsorption

- Causes
  - Jejunal bypass surgery
  - Modern gastric bypass surgery (Roux-en Y gast bypass)
  - Inflammatory Bowel Disease (need intact colon)
  - Pancreatic insufficiency
  - Illeal resection
  - ?Zetia



Malabsorption of bile acids from the diseased or resected terminal ileum → decreased bile acid pool → fat malabs. Colonic bacteria metabolize fats to free FAs, which bind calcium, liberating the more easily absorbed noncalcified oxalate. Also, colonic permeability to oxalate is increased by bile acids and free fatty acids.

3) Primary oxalosis (1ry hyperoxaluria):

- rare **AR disorder**
- **>100mg/day of oxalate**
- **C/P:**
  - increased deposition of calcium oxalate in the kidneys
  - → aggressve stone formation, nephrocalcinosis up to ESRD
  - ESRD → calcium oxalate deposition in other tissues
- Diagnosis:
  - laboratory findings of severe hyperoxaluria and clinical symptoms
  - definitive diagnosis requires **liver biopsy** to assay the enzyme activity.
- Mech:
  - Deficient two liver enzymes of oxalate metabolism
  - prevents conversion of glyoxylate to glycine
  - So glyoxalate converted to oxalate instead (in liver)
- Types:
  - type 1 = **lack of AGT** enzyme (liver)
  - type 2 = lack of glyoxylate reductase (liver) } less aggressive course without renal failure
- ttt:
  - liver-kidney Tx,
  - If un-Rx'd →50% ESRD by age 15 (with ~30% death rate)

4) idiopathic

ttt: General measures + restriction of dietary oxalate and regular calcium intake. **Pyridoxine** (reduce urine levels, especially in primary hyperoxaluria).

HyperUricemia

See Uric acid stones below

Causes:

1) dietary excess of purines (most common)
2) Uric acid overproduction } gout, myeloproliferative d/o, MM, hemoglobinopathy, etc

=================

Hypomagnesuria

- rare cause of Ca stones } Mg normally complexes with oxalate and Ca
  - associated with low citrate levels
- Mg metabolism:
  - absorbed from large & small bowel (mostly ileum, mainly by passive diffusion
  - regulated by Vit D (increased gut absorption of Mg)
    excreted by kidneys (majority reabsorbed in loop of Henle, not PCT)
- Hypomagnesuria: urinary Mg <40mg/day *(< 3.0 mmol/day)*
- *Causes:*
  - poor dietary intake or reduced intestinal absorption (chronic diarrhoea).

Hypocitraturia.

- Citrate is a urinary stone inhibitor.
- Mech:
  - by binding to calcium
  - by directly inhibiting the growth and aggregation of Ca oxalate & CaPO4 crystals.
- Hypocitraturia
  - Ur. citrate < 320 mg/day (1.5 mmol/day).
  - Ur. citrate < 2.5 mmol/day may be idiopathic or secondary to metabolic acidosis or hypokalaemia.
- Etiology:
  Systemic acidosis is primary determinant of urinary citrate excretion

  1) distal RTA :
     - inability to acidify urine after oral acid load (NH4Cl)
     - high urine pH (>6.8) + hyperCL + hypoK + low serum HCO3 (met acidosis)
  2) diarrheal states: intestinal alkali loss results in systemic acidosis
  3) thiazide-induced: induced hypoK + intracellular acidosis
  4) high-protein diet: acid load (or high salt intake)
  5) idiopathic (un-related to acidotic state)

- **ttt**: General measures +
    - citrate replacement therapy reduces the risk of stone formation but not proved in children.
    - **potassium citrate** (starting dose 1 mEq/kg, in two divided doses).
    - **Factors increase Urinary Citrate:**
        - Alkalotic states
        - Inc. PTH, Vit D, GH
        - Estrogen

Ca Stones

Calcium oxalate stones قراءة سريعة

Diagnosis كما سبق +

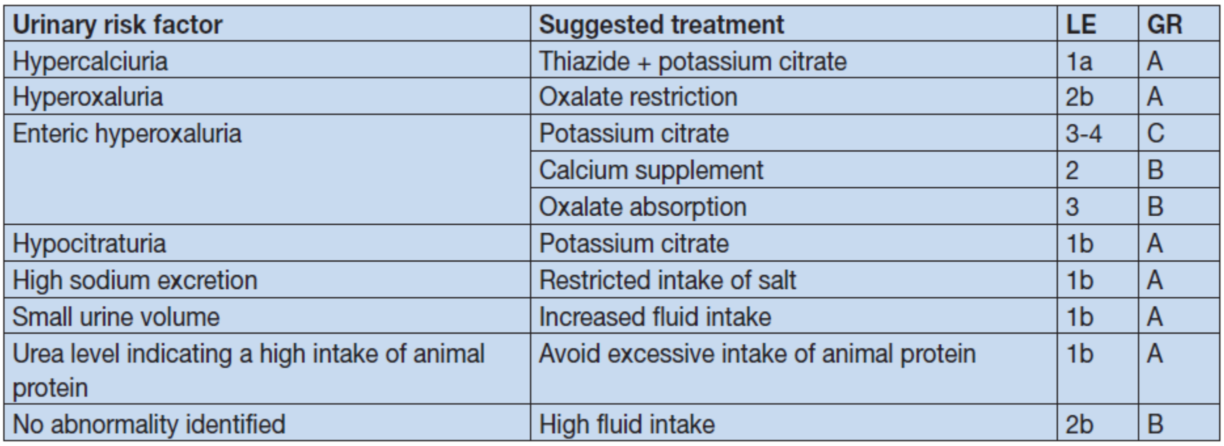
- Blood analysis: Cr, Na, K, Cl, **ionised calcium (or total calcium + albumin)**, uric acid, and **PTH (and vitamin D)** in case of increased calcium levels.
- Urinalysis: urine volume, urine pH profile, specific weight, Ca , oxalate, uric acid, citrate, Na, Mg.

Specific treatment

General measures: +

- Hyperoxaluric: foods with low oxalate content,
- Hyperuricosuric: daily dietary reduction of purine.

Recommendations for pharmacological ttt of pts with specific abn in Ur

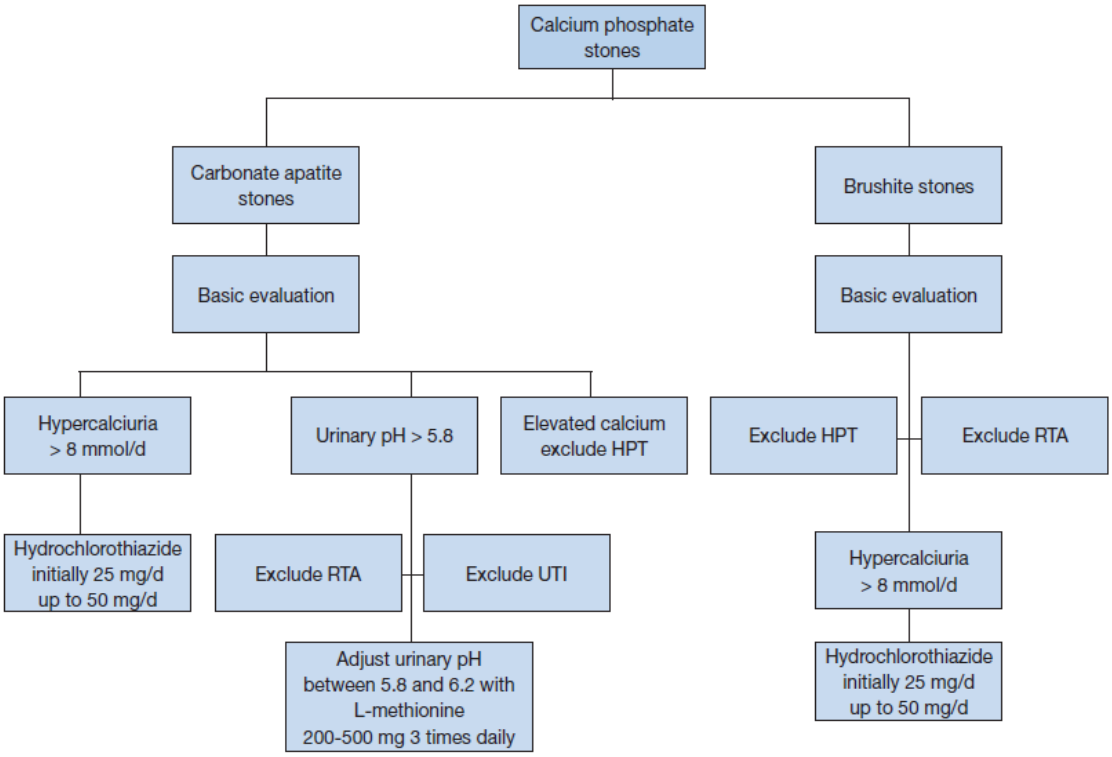


Urinary risk factor	Suggested treatment	LE	GR
Hypercalciuria	Thiazide + potassium citrate	1a	A
Hyperoxaluria	Oxalate restriction	2b	A
Enteric hyperoxaluria	Potassium citrate	3-4	C
	Calcium supplement	2	B
	Oxalate absorption	3	B
Hypocitraturia	Potassium citrate	1b	A
High sodium excretion	Restricted intake of salt	1b	A
Small urine volume	Increased fluid intake	1b	A
Urea level indicating a high intake of animal protein	Avoid excessive intake of animal protein	1b	A
No abnormality identified	High fluid intake	2b	B

Calcium phosphate stones

- PO4 metabolism:
  - 60% of dietary PO4 is absorbed } mostly from small bowel
  - higher absorption with alkaline luminal pH
  - 65% of absorbed PO4 is excreted by kidneys } reabsorbed in tubules (inhibited by PTH)
  - 35% of PO4 excreted by gut
- Some calcium phosphate stone formers at high risk of recurrence.
- Calcium phosphate appears in two different minerals: carbonate apatite and brushite:
  - Carbonate apatite crystallisation occurs at pH ≥ 6.8 and may be associated with infection.
  - Brushite crystallises at an optimum pH of 6.5-6.8, at high urinary concentrations of calcium (> 8 mmol/ day) and phosphate (> 35 mmol/day). not related to UTI.
- Possible causes of calcium phosphate stones include HPT, RTA and UTI; each of which requires different therapy.

Diagnostic and therapeutic algorithm for calcium phosphate stones

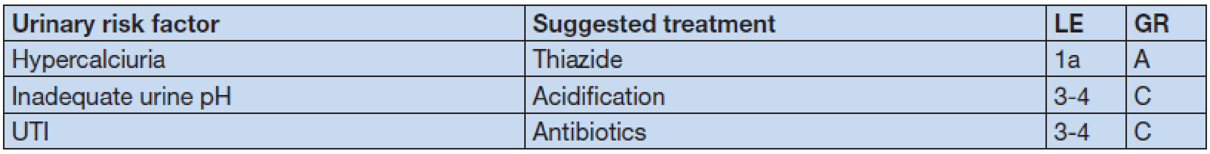

Calcium phosphate stones
Carbonate apatite stones
Brushite stones
Basic evaluation
Basic evaluation
Hypercalciuria > 8 mmol/d
Urinary pH > 5.8
Elevated calcium exclude HPT
Exclude HPT
Exclude RTA
Hydrochlorothiazide initially 25 mg/d up to 50 mg/d
Exclude RTA
Exclude UTI
Hypercalciuria > 8 mmol/d
Adjust urinary pH between 5.8 and 6.2 with L-methionine 200-500 mg 3 times daily
Hydrochlorothiazide initially 25 mg/d up to 50 mg/d

Pharmacological therapy

HPT and RTA are common causes of calcium phosphate stone formation.

- Although most patients with primary HPT require surgery, RTA can be corrected pharmacologically.
- If primary HPT and RTA have been excluded, pharmacotherapy for calcium phosphate calculi depends on effective reduction of urinary calcium levels using thiazides.
- If urine pH remains constantly > 6.2, urinary acidification with l-methionine may be helpful however is not commonly used and needs monitoring for systemic acidosis development.
- For infection-associated calcium phosphate stones, it is important to consider the guidance given for infection stones.

Recommendations for the treatment of calcium phosphate stones



Urinary risk factor	Suggested treatment	LE	GR
Hypercalciuria	Thiazide	1a	A
Inadequate urine pH	Acidification	3-4	C
UTI	Antibiotics	3-4	C

Disorders and diseases related to calcium stones

Hyperparathyroidism

- Primary HPT (5% of all calcium stone formation).
- Kidney stones (20% of patients with primary HPT).
- C/P:
  - bone loss, gastric ulcers and urolithiasis.
  - Elevated levels of PTH significantly increase calcium turnover → hypercalcaemia and hypercalciuria.
- Diagnosis:
  - S.Ca may be mildly elevated,
  - Serum PTH within the upper normal limits, therefore, repeated measurements may be needed; preferably with the patient fasting.
  - Stones of PTH patients may contain both Ca oxalate and Ca phosphate.
- ttt: HPT is suspected, neck exploration should be performed to confirm the diagnosis. Primary HPT can only be cured by surgery.

Granulomatous diseases

- Granulomatous diseases, as sarcoidosis, may be complicated by hypercalcaemia and hypercalciuria 2ry to inc calcitriol production.
- The later is independent of PTH control, leading to increased calcium absorption GIT and suppression of PTH.
- Treatment focusses on the activity of the granulomatous diseases and may require steroids, hydroxychloroquine or ketoconazole. It should be reserved to the specialist.

Primary hyperoxaluria العلاج هنا بتفصيل اكتر شوية

- therapeutic aim: reduce endogenous oxalate production, which is increased in patients with PH.
- **ttt General measures +**
  - **pyridoxine therapy**, normalises or urinary oxalate excretion in 1/3 of pts with PH type I (25mg/kg/d)
  - for preventing calcium oxalate crystallisation include
    - hyperdiuresis,
    - alkaline citrates (9-12g/d)
    - magnesium. (200-400 mg/d)
  - ESRD, primary PH requires simultaneous liver-kidney transplantation.

Enteric hyperoxaluria

- In addition to hyperoxaluria, these patients usually present with hypocitraturia because of loss of alkali.
- Urine pH is usually low, as are urinary calcium and urine volume.
- **ttt:** General measures +
  - restrict oxalate and fat intake
  - **Ca supplement:** enable Caoxalate complex formation **in intestine**
  - **K citrate:** to raise urine PH

Nephrocalcinosis (NC)

- **increased crystal deposition within the renal cortex or medulla, and occurs alone or in combination with kidney stones**.
- Various metabolic causes: HPT, PH, RTA, vit.D met.disorders, idiopathic hypercalciuria and hypocitraturia, and genetic disorders, including Dent's disease Bartter's syndrome and Medullary sponge kidney.

Diagnosis

- Diagnosis requires the following ***blood analysis***: *PTH* (in case of increased calcium levels), *vitamin D and metabolites, vitamin A, sodium, potassium, magnesium, chloride, and blood gas analysis*.
- ***Urinalysis*** should investigate: *urine pH profile* (minimum 4 times daily), *daily urine volume, specific weight of urine, and levels of calcium, oxalate, phosphate, uric acid, magnesium and citrate*.

Ttt:

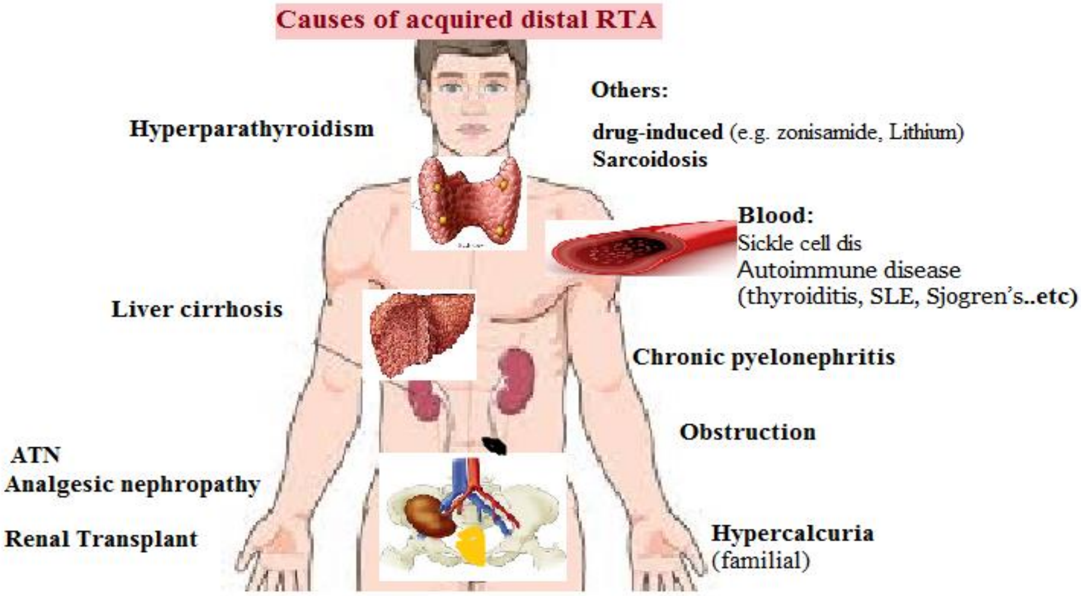
many causes of NC → no single standard therapy. Therapeutic attention focus on underlying metabolic or genetic dis., while minimising the biochemical risk factors.

Renal tubular acidosis:

- Def: family of syndromes due to **defects in renal tubular H+ secretion** & **urinary acidification**
- Etiology: انظر الجدول الكبير ثم الجدول التالي

	Type 1 RTA	Type 2 RTA
1) hypocitraturia	present (stones)	absent (no stones)
2) urine pH	>5.5	N/low urine pH
3) serum HCO3	low	mildly low (15-20)
4) age group	more common in adults	more common in kids

  - severe impairment of proton or bicarbonate handling along the nephron.
  - Acquired or inherited.
  - Kidney stone formation mostly occurs in patients with distal RTA type I.

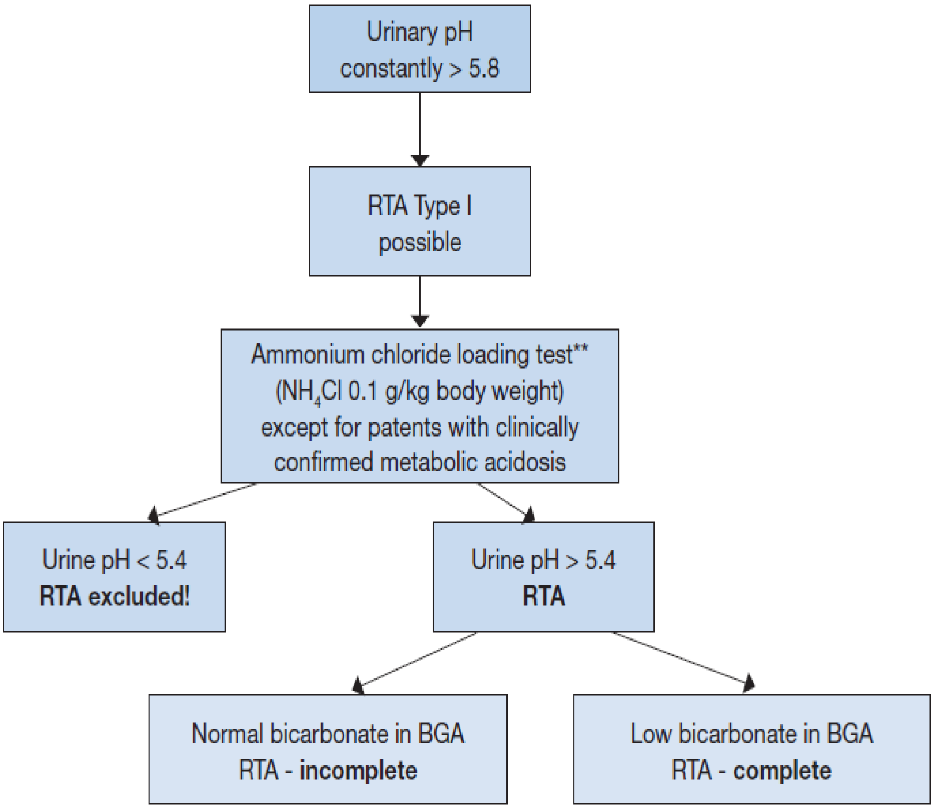

Causes of acquired distal RTA

- Diagnosis: انظر الرسم بالاسفل
  - **Which patients should be evaluated for RTA**:
    - **Urologic Pts**:
      - **B**ilateral stones, **C**aPO4 stones , **R**ecurrent stone formers (>2/yr)
      - **P**yelonephritis (chronic)**,** **A**zotemia
      - **S**ponge kidney } MSK, medullary nephrocalcinosis
    - Others:
      - **I**nfants with FTT
      - **U**nexplained metabolic acidosis (NAG)
      - **D**ecreased K
      - **Hypocitraturia**
  - **Urine pH** levels constantly > 5.8 in the day profile with UTI excluded.
  - **Ammonium chloride loading test** confirms, identifies RTA subtype.

ttt:

- Main therapeutic aim: **restoring a normal acid-base equilibrium**.
    - Despite the alkaline pH of urine in RTA, **alkalinisation using alkaline citrates or sodium bicarbonate** is key to normalising the metabolic changes (intracellular acidosis) responsible for stone formation (Table below).
    - The alkali load reduces tubular reabsorption of citrate, which in turn normalises citrate excretion and simultaneously reduces calcium turnover.
    - Therapeutic success can be monitored by venous blood gas analysis (base excess: ± 2.0 mmol/L) in complete RTA.
- If excessive calcium excretion (> 8 mmol/day) persists after re-establishing acid-base equilibrium, thiazides may lower urinary calcium excretion.

Figure 5: Diagnosis of renal tubular acidosis

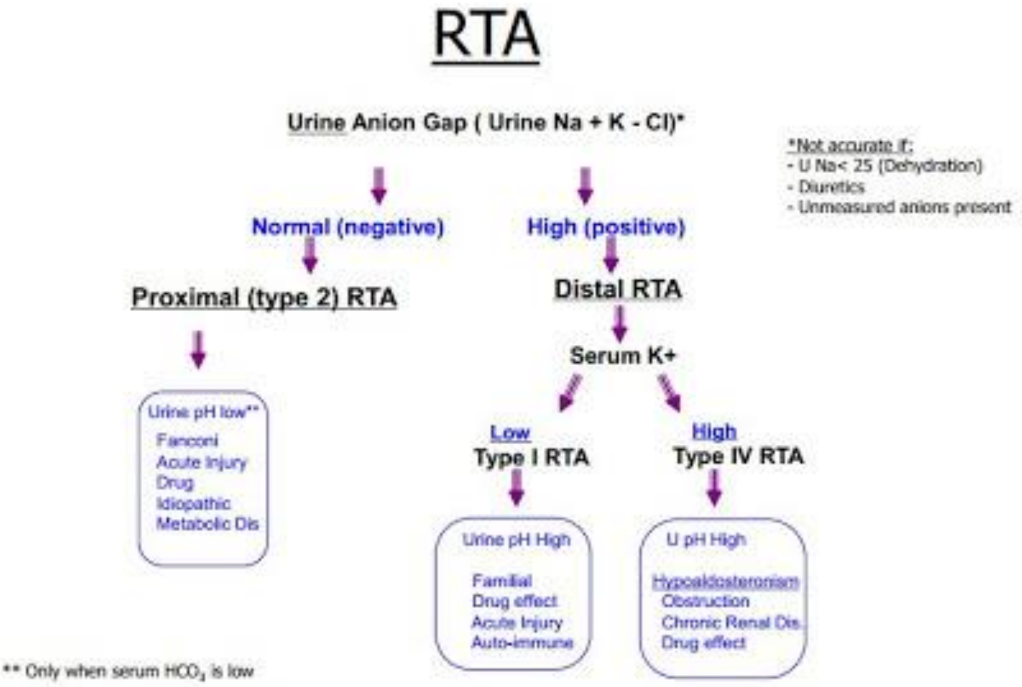

Urinary pH constantly > 5.8
RTA Type I possible
Ammonium chloride loading test** (NH_4Cl 0.1 g/kg body weight) except for patents with clinically confirmed metabolic acidosis
Urine pH < 5.4 **RTA excluded!**
Urine pH > 5.4 **RTA**
Normal bicarbonate in BGA RTA - **incomplete**
Low bicarbonate in BGA RTA - **complete**

*** An alternative Ammonium Chloride loading test using NH4Cl load with 0.05 g/kg body weight over 3 days might provide similar results and may be better tolerated by the patient (31).*

Table 30: Pharmacological treatment of renal tubular acidosis

Biochemical risk factor	Rationale for pharmacological therapy	Medication
Hypercalciuria	Calcium excretion > 8 mmol/day	Hydrochlorothiazide, - in adults, 25 mg/day initially, up to 50 mg/day - in children, 0.5-1 mg/kg/day
Inadequate urine pH	Intracellular acidosis in nephron	Alkaline citrate, 9-12 g/day devided in 3 dosages OR Sodium bicarbonate, 1.5 g, 3 times daily

Urinary risk factor	Suggested treatment	LE	GR
Distal RTA	Potassium citrate	2b	B
Hypercalciuria	Thiazide + potassium citrate	1a	A



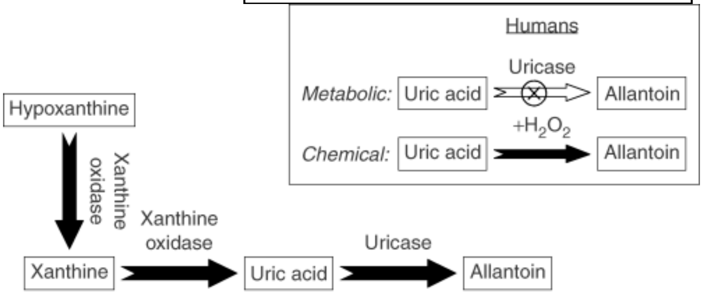
Uric acid and Ammonium Urate stones:

All uric acid and ammonium urate stone formers are considered to be at high risk of recurrence

Uricase (not in humans): enzyme that catalyzes the conversion of uric acid to allantoin more soluble in urine

Uric acid metabolism:

- Uric acid is the end product of purine metabolism. Uric acid ~ 10% of kidney stones. Uric acid stones ~ 4-8% of children.



- importance of urine pH in uric acid stone formation:
  - **urine pH is critical factor in determining uric acid solubility**
  - **most patients with uric acid stones have: acidic urine + N urinary uric acid levels**
    - at pH <5.5, even low concentrations of uric acid are >Kf
    - at pH >6.5, even concentrations of uric acid >1200mg/L remain soluble (<Kf)
    - patients with acidic urine **can also form Ca oxalate stones** } heterogeneous nucleation
- Metabolic defects are seen in Gout pts: (**20% have uric acid stones**)
    - impaired renal production of NH4 } **acidic urine**
    - overproduction of uric acid
    - impaired renal uric acid secretion

→ most gouty diathesis Pts: N urinary levels of uric acid BUT with acidic urine

- **DDx of hyperuricemia:**

  - high cell turnover states } myeloproliferative d/o’s, chemo, RADs, etc
  - primary gout
  - ↑’d activity of 5-phosphoribosyl-1-pyrophosphate synthetase

  - sarcoidosis
  - CRF

  - Lesch-Nyhan disease
  - endocrine dysfunction (eg DM)
  - EtOH’ic & starvation ketoacidosis

  - meds } ASA, HCTZ, cyclosporine, ethambutol, etc

Uric acid stones

- **Hyperuricosuria:** >10 mg/kg/day

- **Determinants of uric acid stone formation:**

(no known inhibitors of uric acid crystallization)

1) **Low urine PH** (ie "gouty diathesis"): **most important factor**

➔ **most have N urinary uric acid + acidic urine pH**

- Uric acid dissociation and solubility is strongly reduced at pH < **5.8**
- Caused by:
  - decreased urinary ammonium excretion → more free H+ → acidic urine (with insulin resistance, obesity or gout),
  - increased endogenous acid production (insulin resistance, metabolic syndrome, or exersice-induced lactic acidosis),
  - increased acid intake (high animal protein intake), or increased base loss (diarrhoea).
- associated with loss of diurnal variation in urinary pH
  - loss of usual alkalinization of urine seen in am & post-prandially

2) **hyperuricosuria**

➔ **differs from gouty patients: hyperuricosuria + N urine pH**

- urinary uric acid >600mg/day
- predisposes to uric acid stones AND Ca oxalate stones
  - dietary excess of purines
  - uric acid overproduction:

    gout, myeloproliferative & lymphoproliferative disorders, multiple myeloma (MM), hemolytic disorders, hemoglobinopathies & thalassemia, etc
- stone formers w/ hyperuricosuria have higher rates of stone formation & more severe symptoms

3) **low urinary volume**

- low urinary volumes increase risk of uric acid supersaturation eg dehydration

- **causes of uric acid stones?**
  1) congenital
     - abnormal renal tubular urate transport
     - abnormal uric acid metabolism eg Lesch-Nyhan syndrome
  2) acquired
     - chronic diarrhea
     - volume depletion
     - myeloproliferative disorders
     - high animal protein diet
     - uricosuric drugs
  3) idiopathic
     - Obesity

- **RFs for uric acid stone formation:**
  1) **G**out
  2) **P**urine-rich diet, red meat

  3) **T**halassemia
  4) **M**yeloproliferative disorders
  5) **N**eoplastic disease
  6) **L**esch-Nyhan syndrome

  7) **O**besity, Pregnancy
  8) **D**M
  9) **D**ehydration (diarrhea, colectomy, ileostomy, etc)

- Diagnosis:
  - Uric acid stones are non-opaque stones. Plain X-rays are insufficient to show uric acid stones, and renal sonography and spiral CT are used for diagnosis.
- ttt:
  - Alkalinisation of urine is the mainstay of therapy and prevention for uric acid stones. **Citrate preparations** are useful as alkalinising agents.
  - Maintaining a urine pH of 6 to 6.5 is sufficient to prevent uric acid stones.

Ammonium urate stones

- are extremely rare, comprising < 1% of urinary stones.
- They are associated with UTI, malabs (IBD and ileostomy diversion or laxative abuse), K deficiency, hypokalemia and malnutrition.

Diagnosis

- Blood analysis requires measurement of creatinine, potassium and uric acid levels.
- Urinalysis requires measurement of urine volume, urine pH profile, specific weight of urine, and uric acid level. **Urine culture** is needed in case of ammonium urate stones.

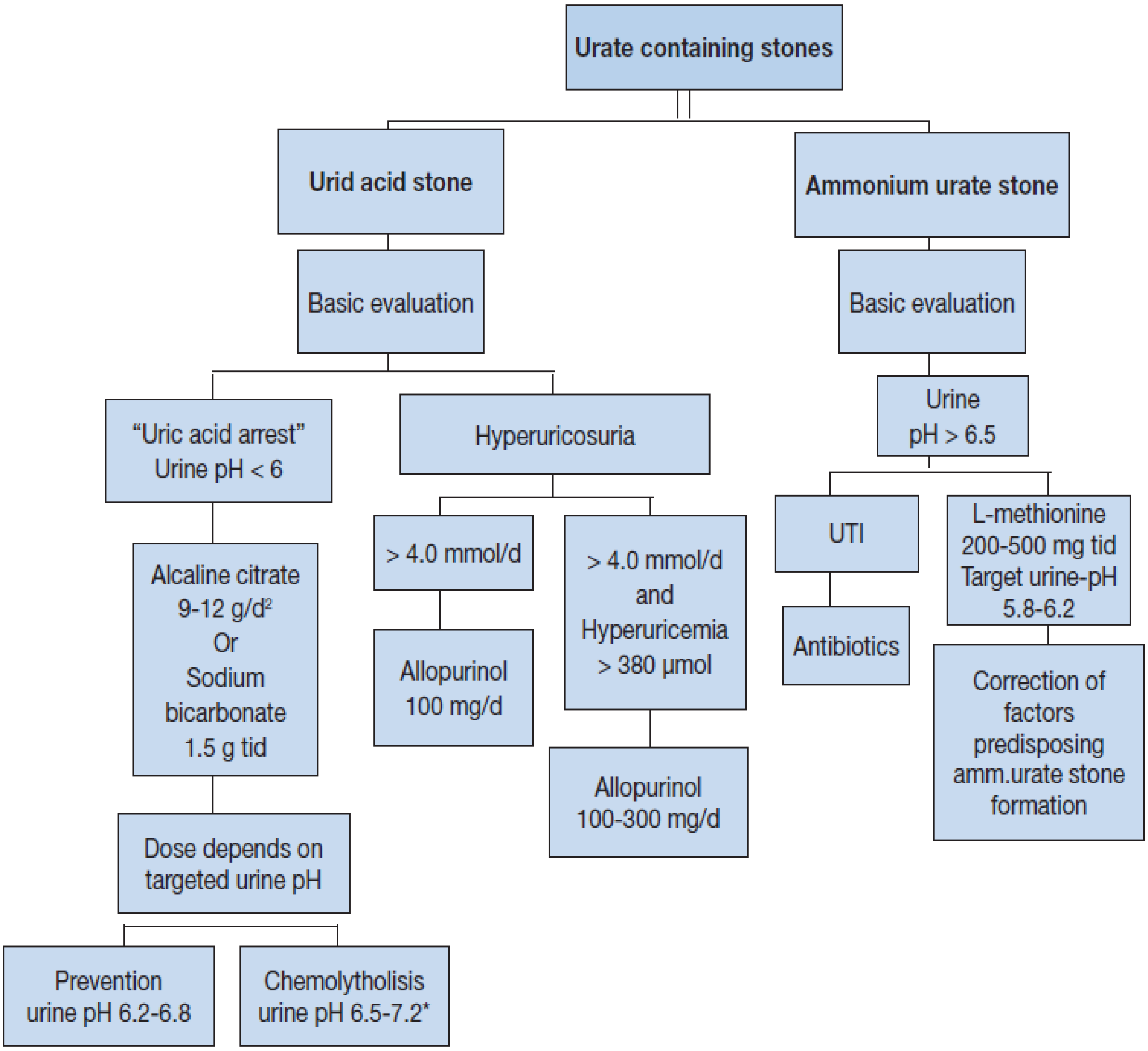
Interpretation of results

- Uric acid and ammonium urate stones form under completely different biochemical conditions. Acidic arrest (urine pH constantly < 5.8) promotes uric acid crystallisation.
- ***Hyperuricosuria*** is defined as **uric acid excretion ≥ 4 mmol/day in adults or > 0.12 mmol/kg/day in children**. ***Hyperuricaemia*** may be present, but there is only weak evidence for its association with stone formation.
- Hyperuricosuric calcium oxalate stone formation can be distinguished from uric acid stone formation by:
  - urinary pH, which is usually > 5.5 in calcium oxalate stone formation and < 5.5 in uric acid stone formation and
  - occasional absence of hyperuricosuria in patients with pure uric acid stones.
- Ammonium urate crystals form in urine at pH > 6.5, at high uric acid concentration and ammonium being present to serve as cation.

Specific treatment

General preventive measures are recommended for fluid intake and diet. Hyperuricosuric stone formers benefit from purine reduction of their daily diet.

Diagnostic and therapeutic algorithm for uric acid and ammonium urate stones


Urate containing stones
Urid acid stone
Ammonium urate stone
Basic evaluation
Basic evaluation
"Uric acid arrest" Urine pH < 6
Hyperuricosuria
Urine pH > 6.5
Alcaline citrate 9-12 g/d^2 Or Sodium bicarbonate 1.5 g tid
> 4.0 mmol/d
> 4.0 mmol/d and Hyperuricemia > 380 µmol
UTI
L-methionine 200-500 mg tid Target urine-pH 5.8-6.2
Allopurinol 100 mg/d
Antibiotics
Correction of factors predisposing amm.urate stone formation
Allopurinol 100-300 mg/d
Dose depends on targeted urine pH
Prevention urine pH 6.2-6.8
Chemolytholisis urine pH 6.5-7.2*

** A higher pH may lead to calcium phosphate stone formation*

Struvite and infection stones

Mg NH4 PO4 stones } may also contain carbonate apatite (CaPO4CO3)

- Incidence: (2-15%) (may originate de novo or grow on pre-existing stones)
    - forms in **alkaline urine (pH>7.2)** with NH3 in urine
    - more common in women (2:1)
    - can grow rapidly → forming staghorn stones
    - High risk of recurrence
- **Causative organism:**
    - only in association with UTI by **urea-splitting bacteria**(urease-forming bugs)
    - most commonly Proteus, Klebsiella, Pseudomonas, corynebacterium and Staph
        - **Proteus mirabilis is most common**
    - **forms in alkaline urine (pH>7.2) with NH3 in urine**
    - E. coli does NOT produce urease BUT can still be associated with stones:
        1) inhibits activity of stone inhibitors such as urokinase & sialidase
        2) injury to urothelium allows crystal adherence
- Pathogenesis:
    - Urease converts urea into ammonia and bicarbonate, so alkalinizing the urine and further converting bicarbonate into carbonate.
    - In alkaline environment, triple phosphates form → supersaturated with magnesium ammonium phosphate and carbonate apatite → stone formation.
- **Most common composition of staghorn stones:**
    1) **Struvite } 67%**
    2) Cystine
    3) uric acid
    4) COM

    isolated CaPO4 is likely the least common to form staghorn
- **RFs** : those at risk for infections

    - **U**rinary diversion

    - **C**ongenital malformations, **O**bstruction **or** **F**B (Foley) in GU tract

    - **F**emale (2x more), **E**lderly- **P**remature infants, **D**M

    - **N**eurologic disorders

- C/P:
  - weakness, malaise, loss of appetite, fever
  - LUTS +/- hematuria, dysuria
  - flank pain - staghorn stone
  - XGP
- ***Diagnosis***
  - Blood analysis requires measurement of creatinine, and urinalysis requires repeat urine pH measurements and urine culture.
  - *Interpretation*
    - Infection stones contain the following minerals: struvite and/or carbonate apatite and/or ammonium urate.
  - Urine culture typically provides evidence for urease-producing bacteria, which increase ammonia ions and develop alkaline urine
    - Carbonate apatite starts to crystallise at a urine pH level of 6.8. Struvite only precipitates at pH > 7.2. **Proteus mirabilis** accounts for more than half of all urease-positive UTIs.
  - Consideration should be given to investigating any congenital problem that causes stasis and infection. Genitourinary tract anomalies predispose to formation of such stones.

Specific treatment

- General preventive measures recommended for fluid intake and diet.
- Specific measures include:
  - complete surgical stone removal,
  - short- or long-term antibiotic treatment,
  - urinary acidification using methionine or ammonium chloride , and
  - urease inhibition.
- For severe infections, ***acetohydroxamic acid*** may be an option.
- In addition to bacterial elimination, stone elimination is essential for treatment, as stones will harbour infection and antibiotic treatment will not be effective.

11.8.3 *Recommendations for therapeutic measures of infection stones*

Recommendations for therapeutic measures	LE	GR
Surgical removal of the stone material as completely as possible	3,4	A*
Short-term antibiotic course	3	B
Long-term antibiotic course	3	B
Urinary acidification: ammonium chloride, 1 g 2 or 3 times daily	3	B
Urinary acidification: methionine, 200-500 mg, 1-3 times daily	3	B
Urease inhibition	1b	A

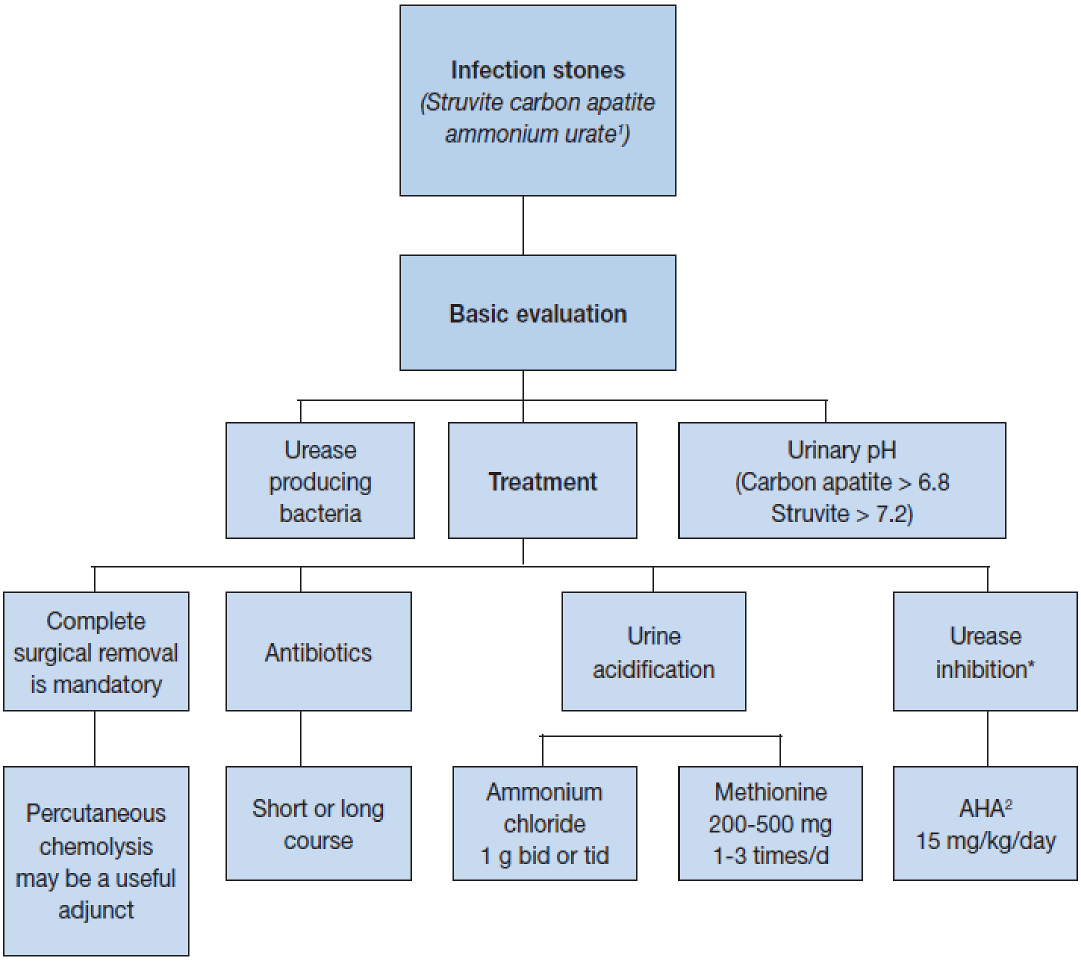
Table 31: Factors predisposing to struvite stone formation

Neurogenic bladder
Spinal cord injury/paralysis
Continent urinary diversion
Heal conduit
Foreign body
Stone disease
Indwelling urinary catheter
Urethral stricture
Benign prostatic hyperplasia
Bladder diverticulum
Cystocele
Caliceal diverticulum
Ureteropelvic junction obstruction

Table 32: Most important species of urease-producing bacteria

Obligate urease-producing bacteria (> 98 %)
• *Proteus spp.* • *Providencia rettgeri* • *Morganella morganii* • *Corynebacterium urealyticum* • *Ureaplasma urealyticum*
Facultative urease-producing bacteria
• *Enterobacter gergoviae* • *Klebsiella spp.* • *Providencia stuartii* • *Serratia marcescens* • *Staphylococcus spp.*
CAUTION: 0-5% of strains of *Escherichia coli*, *Entercoccus spp*. and *Pseudomonas aeruginosa* may produce urease.

Figure 7: Diagnostic and therapeutic algorithm for infection stones


Infection stones
(Struvite carbon apatite ammonium urate1)
Basic evaluation
Urease producing bacteria
Treatment
Urinary pH (Carbon apatite > 6.8 Struvite > 7.2)
Complete surgical removal is mandatory
Antibiotics
Urine acidification
Urease inhibition*
Percutaneous chemolysis may be a useful adjunct
Short or long course
Ammonium chloride 1 g bid or tid
Methionine 200-500 mg 1-3 times/d
AHA2 15 mg/kg/day

[1] *Discussed with uric acid stones, 4 acetohydroxamic acid*

** When nationally available.*

Cystine stones

Cystine stones account for 1-2% of all urinary stones in adults and 6-8% of the stones reported in paediatric studies. All cystine stone formers are deemed at high risk of recurrence.

- Def. of **Cystinuria**
  - **AR disorder** characterized by a defect in intestinal & renal PCT transport of dibasic amino acids → **cystine, ornithine, lysine, arginine (COLA)**
  - high urinary concentrations of each BUT only cystine is poorly soluble (especially in acidic urine).
  - Cystine solubility is pH-dependent, with cystine precipitation beginning at pH levels < 7.0.
  - rare cause of stones in adults (<1%), more in kids (~10%)
  - **3 types of cystinuria**
    - type A (chromosome 2 mutation)
    - type B (chromosome 19 mutation)
    - type AB (chromosome 2 & 19 mutations)

    → type B has higher urinary cystine } but SAME RATE OF STONES
  - average age at Dx is ~12yrs
  - stone episode usually every 2-5 yrs\
- Other metabolic conditions, such as hypercalciuria, hypocitraturia and hyperuricosuria, may accompany cystinuria, so leading to the formation of mixed-composition stones.
- ***Diagnosis***
  - Blood analysis includes measurement of creatinine, and urinalysis includes measurement of urine volume, pH profile, specific weight, and cystine.

Interpretation

- Cystine is poorly soluble in urine and crystallises spontaneously within the physiological urinary pH range.
- Routine analysis of cystine is not suitable for therapeutic monitoring.
- Diagnosis is established by stone analysis. The typical hexagonal crystals are detectable in only 20-25% of urine specimens from patients with cystinuna.
- ***The cyanide nitroprusside colonmetric qualitative test*** detects the presence of cystine at a threshold concentration of 75 mg/L.
  - False-positive results in patients with Fanconi's syndrome, homocystinuria, or those taking various drugs, including ampicillin or sulfa-containing medication.
- ***Quantitative 24-h urinary cystine excretion*** confirms the diagnosis in the absence of stone analysis. Levels above 30 mg/day are considered abnormal.

- ***Specific treatment***
  - General preventative measures for fluid intake and diet are recommended.
    - A diet low in methionine may theoretically reduce urinary excretion of cystine,
    - A restricted intake of sodium is more effective in reducing urinary cysteine (avoid sodium consumption > 2 g/day).
    - A high level of diuresis is of fundamental importance, aiming for a 24-h urine volume of $\geq$3 L.
    - A considerable fluid intake evenly distributed throughout the day is necessary.

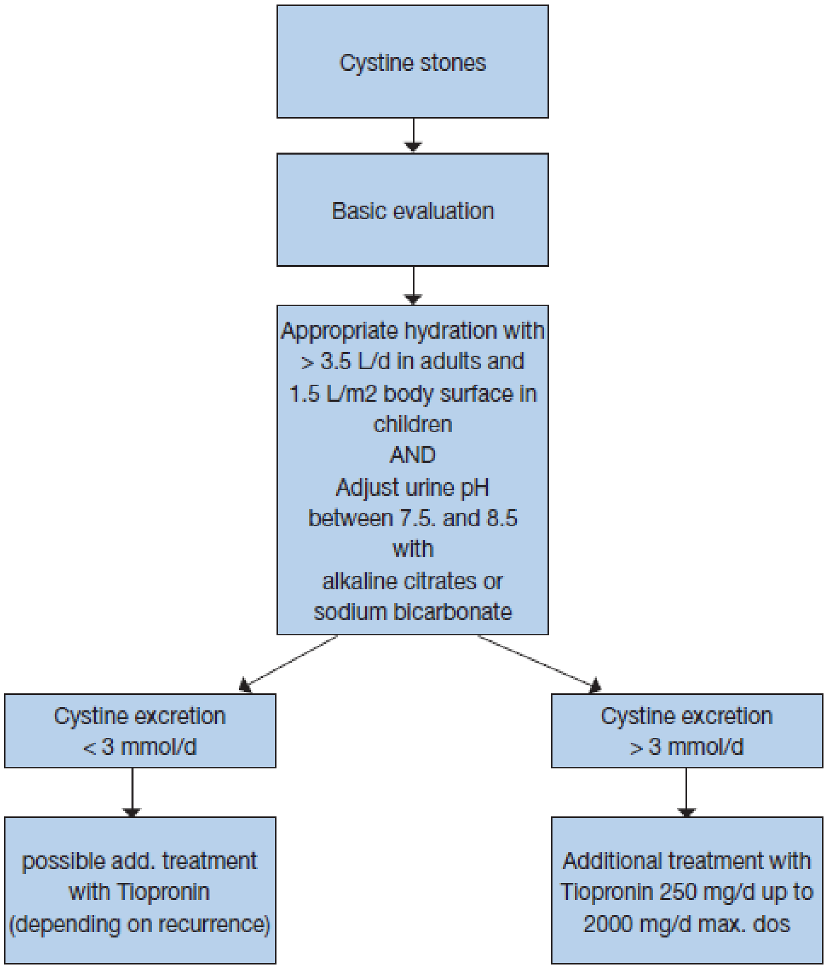
Pharmacological treatment of cystine stones

- The main therapeutic option for avoiding cystine crystallisation is to **maintain urine pH > 7.5** (alkalinising agents, such as potassium citrate), to improve cystine solubility and ensure ***appropriate hydration*** with a minimum of 3.5 L/day in adults, or 1.5 L/m^2 body surface area in children

Use of these drugs can be associated with severe side effects, such as bone marrow depression and nephrotic syndrome.

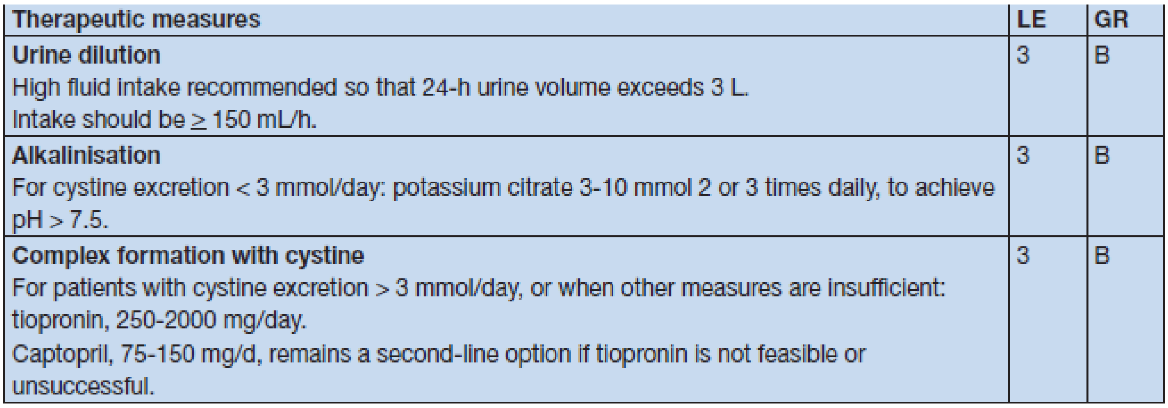
- Free cystine concentration can be decreased by **reductive substances**, which act by splitting the disulphide binding of cysteine.
    - ***Tiopronin** is the best choice for cystine reduction.*
        - *side effects often lead to treatment termination (eg nephritic syndrome develops,* tachyphylaxis *or poor compliance)*
        - recommended at cystine levels > 3.0 mmol/day or in the case of reccuring stone formation, notwithstanding other preventive measures.
    - **Ascorbic acid** (as effervescent tablets) can be used when cystine excretion is < 3.0 mmol/day (controversial).
    - **angiotensin-converting enzyme inhibitor**, captopril, are controversial, and hypotonus and hyperkalaemia are possible side effects
        - Captopril remains a second-line option, for use when tiopronin is not feasible or unsuccessful.
    - If this treatment fails, the use of **α-mercaptopropionil glycine** may reduce cystine levels in urine and prevent stone formation.

Metabolic management of cystine stones


Cystine stones
Basic evaluation
Appropriate hydration with > 3.5 L/d in adults and 1.5 L/m2 body surface in children AND Adjust urine pH between 7.5. and 8.5 with alkaline citrates or sodium bicarbonate
Cystine excretion < 3 mmol/d
Cystine excretion > 3 mmol/d
possible add. treatment with Tiopronin (depending on recurrence)
Additional treatment with Tiopronin 250 mg/d up to 2000 mg/d max. dos

- Cystine stones are faintly radiolucent and may be difficult to show on regular radiograph studies. They are also hard in texture and more difficult to disintegrate by extracorporeal shock wave lithotripsy (SWL).

Recommendations for the treatment of cystine stones



Therapeutic measures	LE	GR
Urine dilution High fluid intake recommended so that 24-h urine volume exceeds 3 L. Intake should be ≥ 150 mL/h.	3	B
Alkalinisation For cystine excretion < 3 mmol/day: potassium citrate 3-10 mmol 2 or 3 times daily, to achieve pH > 7.5.	3	B
Complex formation with cystine For patients with cystine excretion > 3 mmol/day, or when other measures are insufficient: tiopronin, 250-2000 mg/day. Captopril, 75-150 mg/d, remains a second-line option if tiopronin is not feasible or unsuccessful.	3	B

2,8-dihydroyadenine stones and xanthine stones

– high risk of recurrence. Both stone types are rare. Diagnosis and specific prevention are similar to those for uric acid stones.

2,8-dihydroxyadenine stones

– A genetically determined ***defect of adenine phosphoribosyl transferase*** causes high urinary excretion of poorly soluble 2,8-dihydroxyadenine.

– ttt: High-dose allopurinol or febuxostat are important options, but should be given with regular monitoring.

Xanthine stones

– Patients who form xanthine stones usually show decreased levels of serum uric acid. There is no available pharmacological intervention.

Fluid intake and diet

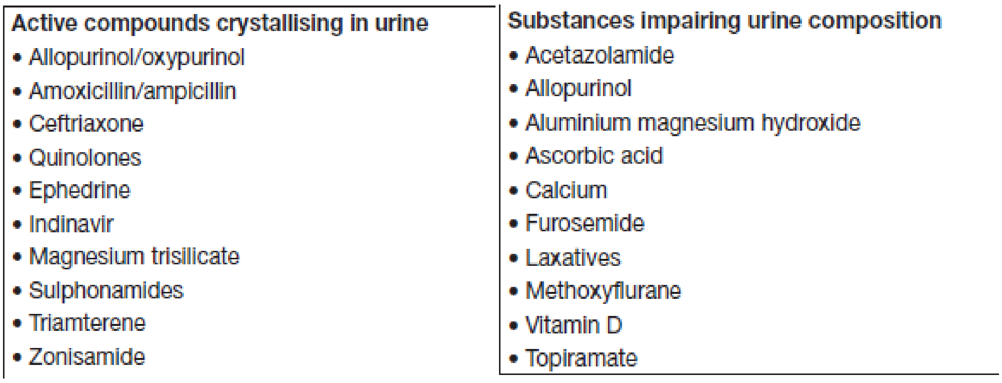
– Recommendations for general preventive measures apply. Pharmacological intervention is difficult, therefore, high fluid intake ensures optimal specific weight levels of urine < 1.010. A purine-reduced diet decreases the risk of spontaneous crystallisation in urine.

Drug stones

Drug stones are induced by pharmacological treatment (Table 33). Two types exist:

- stones formed by crystallised compounds of the drug;
- stones formed due to unfavourable changes in urine composition under drug therapy.

Table 33: Compounds that cause drug stones



Active compounds crystallising in urine	Substances impairing urine composition
• Allopurinol/oxypurinol	• Acetazolamide
• Amoxicillin/ampicillin	• Allopurinol
• Ceftriaxone	• Aluminium magnesium hydroxide
• Quinolones	• Ascorbic acid
• Ephedrine	• Calcium
• Indinavir	• Furosemide
• Magnesium trisilicate	• Laxatives
• Sulphonamides	• Methoxyflurane
• Triamterene	• Vitamin D
• Zonisamide	• Topiramate

What are some medication-related stones?

1) **meds that directly form stones (ALL RADIOLUCENT)** }}} "Silicates GET SIC"
    - **Silicates** (eg Mg silicate antacids) → stones form w/ consumption of large amounts
    - Guaifenesin (expectorant) → metabolite forms stone
    - Ephedrine (cold meds, herbal ecstasy, Ma Huang, etc) → metabolite forms stones
    - Triamterene (K+ sparing diuretic) → usually incorporates onto existing stone/nidus
      → doesn't usually form pure triamterene stone
      (triamterene or its sulfate metabolite)
    - Septra (TMP-SMX)
    - Indinavir (protease inhibitor) → high urinary excretion & poor solubility at N urine pH
      → more soluble at pH <5.5
      → radiolucent even on CT
    - Cipro
2) **meds that indirectly promote stone formation** }}} "Can PLATE FAST"
    - Cytotoxic agents → high cell turnover and increased uric acid stones
    - PO4-binding antacids → hypercalciuria
    - Laxatives → persistent diarrhea leads to ammonium acid urate stones
    - Acetazolamide (carbonic anhydrase inhibitor) → metabolic acidosis + urinary alkalinization,
      → results in hypocitraturia (CaPO4 stones)
    - Thiazides → intracellular acidosis and subsequent hypocitraturia
    - Excess Vit D → hypercalciuria
    - Furosemide → hypercalciuria
    - Allopurinol → high doses can lead to xanthine stones
    - Steroids → hypercalciuria
    - Topiramate (antiepileptic) → acts like a carbonic anhydrase inhibitor

Matrix stones

- **radiolucent stones**
- often confused with tumour or uric acid stones
- by weight, composed of **2/3 mucoprotein and 1/3 mucopolysaccharide**
    - pure matrix stone made of 65% matrix protein
    - usually matrix component of Ca stones represent only ~2.5% of weight
- may be associated with low urine Ca or proteinuria (renal failure patients).

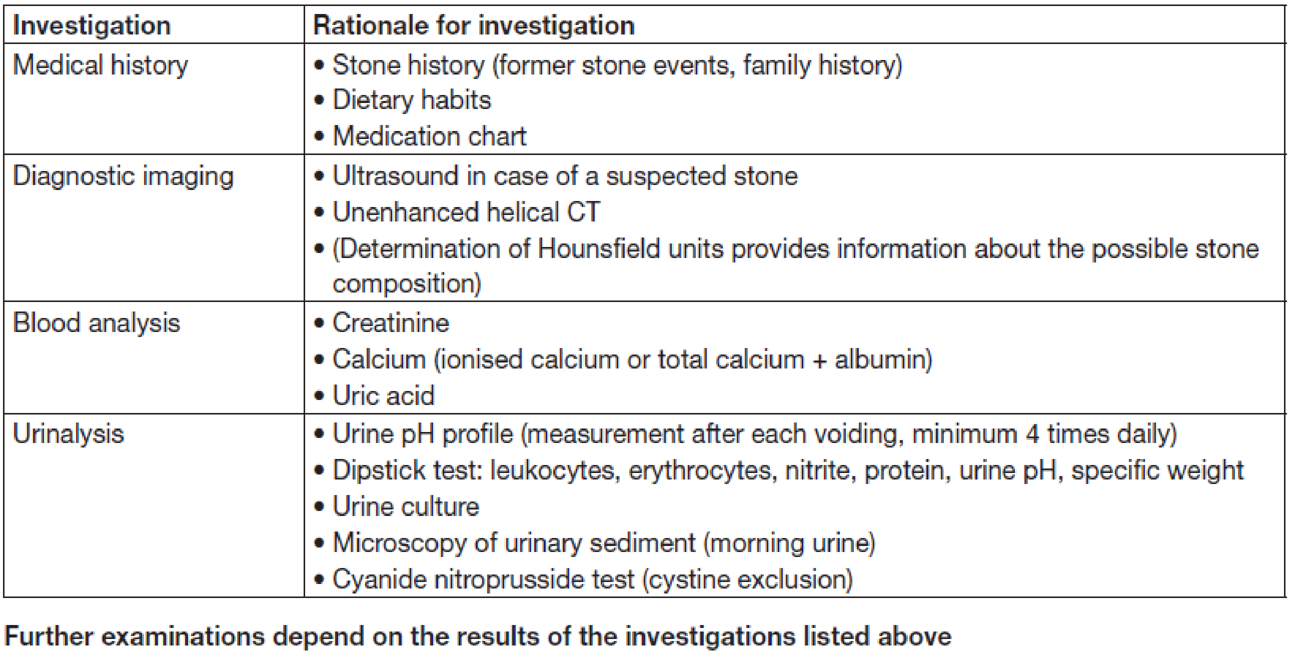
Unknown stone composition

- An accurate medical history is the first step towards identifying risk factors
- Diagnostic imaging begins with ultrasound examination of both kidneys to establish whether the patient is stone free. Stone detection by ultrasound should be followed by KUB and unenhanced multislice CT in adults to differentiate between calcium-containing and non-calcium stones.
- Blood analysis demonstrates severe metabolic and organic disorders, such as renal insufficiency, HPT or other hypercalcaemic states and hyperuricaemia. In children, hyperoxalaemia is additionally screened.

- Urinalysis is performed routinely with a dipstick test as described above. Urine culture is required if there are signs of infection.
- Constant urine pH < 5,8 in the daily profile indicates acidic arrest, which may promote uric acid crystallisation. Persistent urine pH > 5.8 in the daily profile indicates RTA, if UTI is excluded.
- Microscopy of urinary sediment can help to discover rare stone types, because crystals of 2,8-dihydroxyadenine, cystine and xanthine are pathognomonic for the corresponding disease.
    - In cases in which the presence of cystine is doubtful, a cyanide nitroprusside colorimetric qualitative test can be used to detect the presence of cystine in urine.
    - False-positive results are possible in patients with Fanconi's syndrome or homocystinuria, or in those taking various drugs, including ampicillin or sulfa-containing medication.

- Following this programme, the most probable stone type can be assumed and specific patient evaluation can follow. However, if any expulsed stone material is available, it should be analysed by diagnostic confirmation or correction.

Investigating patients with stones of unknown composition



Investigation	Rationale for investigation
Medical history	• Stone history (former stone events, family history) • Dietary habits • Medication chart
Diagnostic imaging	• Ultrasound in case of a suspected stone • Unenhanced helical CT • (Determination of Hounsfield units provides information about the possible stone composition)
Blood analysis	• Creatinine • Calcium (ionised calcium or total calcium + albumin) • Uric acid
Urinalysis	• Urine pH profile (measurement after each voiding, minimum 4 times daily) • Dipstick test: leukocytes, erythrocytes, nitrite, protein, urine pH, specific weight • Urine culture • Microscopy of urinary sediment (morning urine) • Cyanide nitroprusside test (cystine exclusion)

Further examinations depend on the results of the investigations listed above

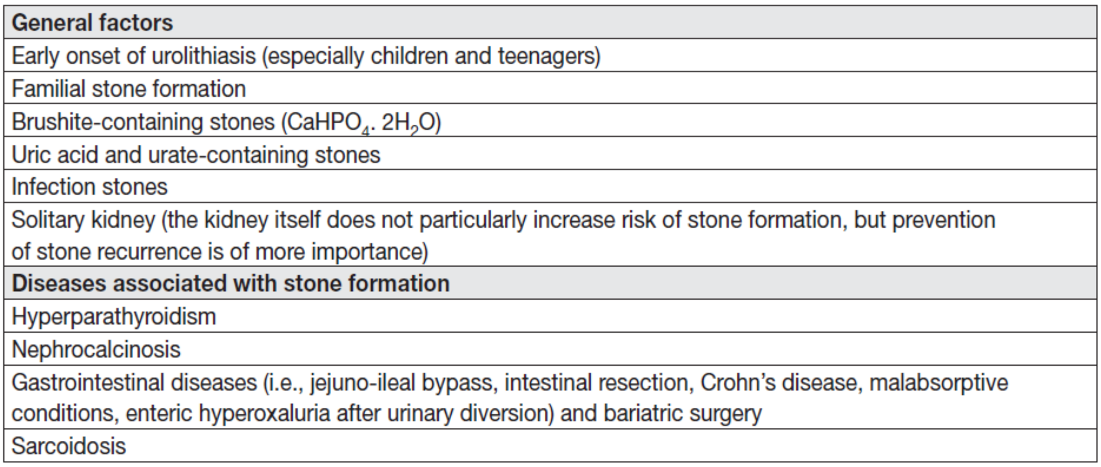
زيادات

- The risk status of stone formers is of particular interest because it defines the probability of recurrence or regrowth, and is imperative for pharmacological treatment.

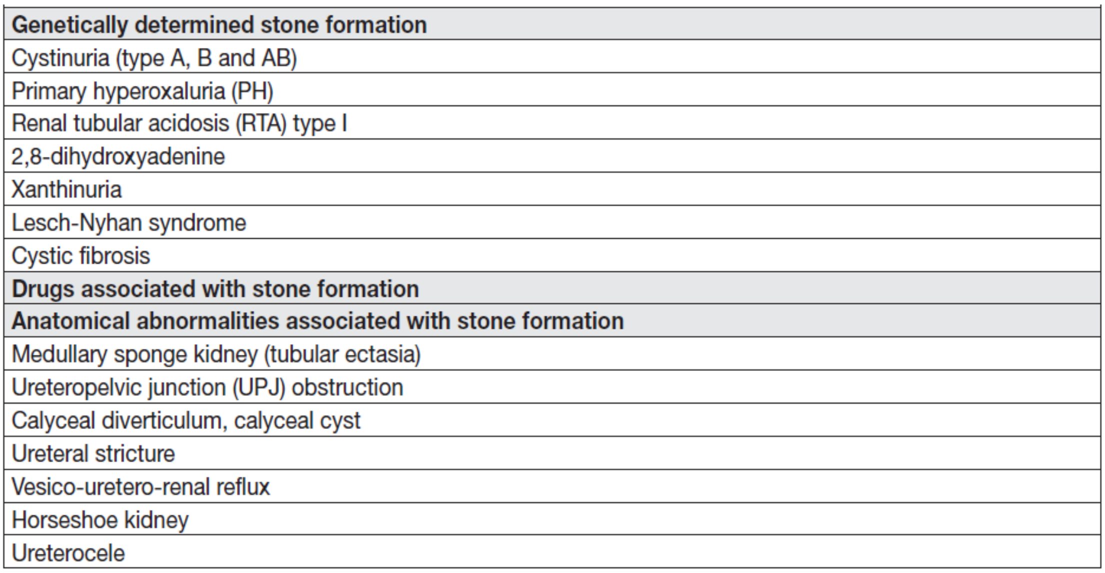
- About 50% of recurrent stone formers have just one lifetime recurrence.

- Highly recurrent disease is observed in slightly more than 10% of patients. Stone type and disease severity determine low or high risk of recurrence (Table 6)

Table 6: High-risk stone formers (6-12)



General factors
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
Brushite-containing stones ($CaHPO_4 . 2H_2O$)
Uric acid and urate-containing stones
Infection stones
Solitary kidney (the kidney itself does not particularly increase risk of stone formation, but prevention of stone recurrence is of more importance)
Diseases associated with stone formation
Hyperparathyroidism
Nephrocalcinosis
Gastrointestinal diseases (i.e., jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion) and bariatric surgery
Sarcoidosis



Genetically determined stone formation
Cystinuria (type A, B and AB)
Primary hyperoxaluria (PH)
Renal tubular acidosis (RTA) type I
2,8-dihydroxyadenine
Xanthinuria
Lesch-Nyhan syndrome
Cystic fibrosis
Drugs associated with stone formation
Anatomical abnormalities associated with stone formation
Medullary sponge kidney (tubular ectasia)
Ureteropelvic junction (UPJ) obstruction
Calyceal diverticulum, calyceal cyst
Ureteral stricture
Vesico-uretero-renal reflux
Horseshoe kidney
Ureterocele